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A. P. LEMBERGER

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PROCEEDINGS OF THE TEACHERS' SEMINAR ON PHARMACY

THE TECHNICAL PHARMACY COURSES

PROLOGUE

SYLLABUS FOR INSTRUCTION IN PHARMACY

CURRENT CONCEPTS IN SELECTED SUBJECT AREAS

PROCEEDINGS OF THE TEACHERS' SEMINAR ON PHARMACY

MADISON, WISCONSIN, 1961

THE TECHNICAL PHARMACY COURSES

PROLOGUE

GREETINGS FROM THE UNIVERSITY OF WISCONSIN

PRES. CONRAD A. ELVEHJEM

I want to bid you official welcome on behalf of the University and give you my own best wishes for a productive and pleasant visit.

If my facts are right, this series of seminars for teachers in the various pharmacy fields started here on this campus in 1949. We welcome your return, and hope that you will want to be back with us soon again.

As most of you probably know, pharmacy holds an important place on this campus and has held it for years, even before one of Wisconsin's most prominent pharmacists became governor of our state and later regent of the University.

As the first institution to offer graduate work in pharmacy in the country, Wisconsin feels a particular responsibility for pharmacy teaching. Many of you, I suspect, did graduate work on this campus.

We are particularly proud of our history of pharmacy library collections and I understand that the fascinating display of books—many of them from our Thordarson Collection on the history of science—and artifacts of pharmacy, which was set up for sessions of the American Institute on the History of Pharmacy, have been held on view for your meeting in our Memorial Liibrary.

And at the Historical Library, just across the Mall from our Memorial Library, there is installed a late 19th Century Drug Store which has intrigued me.

Although I am sure that most of your deliberations will be concerned with the forward look in pharmacy, an occasional backward glance is, I believe, helpful to all of us in the sciences, for it gives us some perspective on our place in society and an appreciation for the rapid advancement our fields now are enjoying.

Conferences like this, held annually in one of the pharmacy teaching fields, are testimony to the fact that pharmacy faculties are working to keep abreast of scientific progress. This is extremely important, since pharmacists are a link between the discovery and utilization of knowledge, and the lag between the

laboratory and the consumer must be shortened as scientific progress accelerates. George Urdang in his report on "Pharmacy's Part in Society," published several years ago, pointed up this fact but reminded us of the continuing responsibility of the field in these words:

> "The concepts and aspects of society are changing continuously. The needs which pharmacy is destined to serve, however, are unchangeable. They require people endowed with the knowledge and imbued with the ethics necessary for the adequate fulfillment of their responsible tasks."

And Dr. Urdang concluded:

> "No matter to what extent the form of society may change, pharmacy will always have a part in it."

Again I want to bid you welcome and wish you well. Yours is a vital calling.

GREETINGS FROM THE SCHOOL OF PHARMACY

A. H. UHL

First I want to add my welcome to that of President Elvehjem to all of you here for the Thirteenth Annual Seminar for teachers of pharmacy in our schools and colleges of pharmacy.

It was twelve years ago last January when Dr. Edward Elliott and I were going from Columbus, Ohio, to Washington, D. C. that he discussed with me the need for a program to help our teachers in schools and colleges of pharmacy to become better teachers. Before reaching Washington he struck on the idea of a seminar in the various areas of our teaching program and asked me if we would sponsor a seminar for those responsible for teaching pharmacy. Although it was rather late when I arrived back in Madison to arrange for proper facilities, I presented the idea to the faculty and we decided to go ahead. I will not say more concerning the facilities we made available to the participants. Those of you who were here for this first meeting remember the rooms in the stadium and T–16, along with the 100° temperature.

The development of a program was another matter. Because we had only a vague idea of what type program we were to arrange, it seemed reasonable to develop a rough outline and then go to those who were experienced in methods and techniques of teaching for advice and detail. Our School of Education, and especially Dr. Milton O. Pella, proved to be especially helpful. Each year since, a seminar has been held in one of the five areas of instruction and every sixth year we have been holding a joint seminar where overlapping problems of these areas could be discussed. I thought it would be interesting if you could see a copy of the first seminar program, especially those of you who were not there and to refresh the memories of those who were there.

I sincerely hope that you will find the program that has been arranged both stimulating and challenging and that your teaching will be better thereafter because you have spent this week here. Personally I want to thank those of our faculty especially Gus and Dick who have put much time and effort into making proper arrangements for the meeting. If I can be of help to any of you during the week I hope you will not hesitate to let me know.

GREETINGS FROM THE AMERICAN FOUNDATION FOR PHARMACEUTICAL EDUCATION

W. PAUL BRIGGS

Greeting the annual Pharmacy Teachers' Seminar, on behalf of the American Foundation for Pharmaceutical Education, brings me much personal comfort and renews my confidence in the future. The Foundation is proud of its part in these highly productive sessions for the intellectual refreshment of our teachers.

Pharmacy has weathered two years of attack by well-armed enemies. The profession must be prepared for at least two years more of aggressive assault. Probably this new siege will be of even more violent intensity than the opening struggles of 1960–61. Pharmacy must gather new strength and take new confidences in its vital services as member of the American health team. This new strength and confidence must come from our colleges and more directly, from our dedicated and informed teachers.

To meet these challenges, pharmacy teachers must possess wisdom, knowledge, and skill. They must stimulate interest and provide guide lines and continuous direction for the entire profession. Expertness in the art of communication is not enough—teachers must be playwright, stage manager, and leading actor. Teachers must first organize, and then dramatize facts to promote learning. The good teacher must inspire his students, direct their vision, and start them toward living and livelihood with high moral standards and confidence in the future.

In recommending establishment of these annual seminars, "The Pharmaceutical Survey" said . . . "The effectiveness of any program of education and training depends upon the competency of the teachers. This competency involves, among other attributes, broad and thorough knowledge of the subject matter and skill in teaching. Therefore, consideration of steps for the immediate future should take into account measures for the adoption of the most effective methods of instruction. In fact, any considerable improvement in the . . . program will have to be accomplished largely through greater efficiency in teaching."

The Survey recommendation stated that "The primary purpose of these seminars is that of providing needed opportunity for the members of the teaching staff, and for graduate students to come into fruitful contact and to keep pace with progressive content and methods of pharmaceutical teaching."

These seminars are important factors in the steady movement of pharmaceutical education in the pursuit of excellence. At these sessions I am always especially encouraged to find so many young teachers with the vigor and enthsiasm to carry on. They are the richest resource of pharmacy.

Robert Hutchins says "There is a steady slide toward intellectual inertia. We must commit ourselves to the idea of continuing education throughout our

lives. Education is not a misfortune endured in childhood, which you need not, indeed cannot, have again. Education is the continuous development of our highest powers. It is too good a thing to be left to children."

The seminar is a part of your continuing education and, through you, contributes to the better education of students and continuing training of practitioners of pharmacy. The Foundation is amply rewarded for its part in these seminars by the knowledge that all of pharmacy benefits by the tangible values flowing from these soundly conceived and effective sessions.

Let me commend the University of Wisconsin Seminar Committee for a job well done and add my appreciation for the privilege of being with you.

GREETINGS FROM THE AMERICAN ASSOCIATION OF COLLEGES OF PHARMACY

LLOYD M. PARKS

I am pleased and privileged to attend this Teachers' Seminar on Pharmacy, to bring you greetings from the officers and Executive Committee of the American Association of Colleges of Pharmacy, and to extend best wishes for a fruitful meeting.

I know, from the twenty happy years that I have spent on this campus of the University of Wisconsin, that you will find here the favorable environment for the exchange of ideas that will help to make this Seminar a successful one. You will find here also the recreational facilities for relaxation and enjoyment of fellowship in your free time that contribute significantly to these seminar meetings

We are grateful to the American Foundation for Pharmaceutical Education for its financial support of our *Journal* and other activities of our Association. Without its help this Seminar and many of our other activities could not be carried on. I am sure that I speak for all of us in expressing thanks and appreciation to the Foundation for its continuing interest in and support of pharmaceutical education.

As I studied the program for this Seminar I was impressed by a number of things about it, in addition to the absence of deans. The Seminar is restricted to the technical pharmacy courses and one of its objectives, as advertised in the preliminary outline, is to provide teachers with the latest information and current concepts of selected subjects. Thus, it promises to be a treatment in depth, rather than the "once-over lightly" approach and this, I believe, will be one of its strong points. There should be ample time and opportunity for thorough consideration of the challenging topics that are to be covered. And the decision of the Seminar Committee to avoid the use of specific names, but instead to describe their content and function, in designating the four technical pharmacy courses, should avoid some exercises in semantics.

The liberal use of workshops during the week will, I believe, be another of its strong points. Here will be the opportunity for you, as teachers, to come to grips with your individual teaching problems, to share your strengths and weaknesses, and to learn from your colleagues in the free give and take atmosphere that should prevail. I am a strong believer in workshop sessions of this type because the fruitful interchange which they generate can be of great mutual benefit to everyone.

A successful seminar of this type is characterized by three elements: (1) A statement of the objectives to be achieved; these have been stated in the pre-preliminary outline and will be elaborated on by Dr. Lemberger. (2) A plan designed to achieve those objectives; the plan is evident from the program with which we have been provided. (3) Evaluation to determine if the objectives have been achieved, this element is scheduled for the last session on Friday.

Some ten months ago all of us had the opportunity to express our wishes on the subject matter of this Seminar and to add other comments and suggestions.

In answering that questionnaire I suggested, among other things, that deans should be kept off the "meaty" parts of the program unless they can make contributions as teachers, that they be kept in the background because they have a tendency to monopolize the discussion periods, and that, if necessary, they be used to bring greetings, provide summaries, etc. Little did I realize at that time that my chickens would come home to roost quite so soon! Having made that confession, perhaps I should consider my function on the program fulfilled and retire gracefully at this point. But I cannot resist the opportunity to make some other comments.

May I share with you my concern over an enigma which is very perplexing to me. I do not expect this Seminar to provide the answer; yet it is something that we all should be concerned about in the consideration of our curriculum, what we teach, and how we teach. Simply stated, it is the question, what are we preparing our students for? The problem was outlined in more detail by Grover Bowles in the following excerpt from his recent address as Chairman of the House of Delegates of the American Pharmaceutical Association:

> "Each year, a wave of young pharmacists, well educated and impatient to get ahead, is entering the profession. Many of these young men and women have not 'grown-up' in pharmacy and, in a significant number of cases, have never worked in a pharmacy.
>
> "What happens to these young people?
>
> "Do they find challenging, productive and rewarding careers in pharmacy?
>
> "How many become frustrated and disillusioned because their daily work requires only a portion of their academic background acquired during five years of college? What are we doing to assist those who might be interested in other areas of pharmacy to find their professional niche?"

I am sure that everyone in attendance at this Seminar would agree that our curriculum in pharmacy should prepare our graduates to lead the way in achieving for the pharmacist his proper role in professional practice as we would like to see it, rather than to accept the secondary role to which we see him relegated all too often in actual practice today. We would all agree that the pharmacist should be the expert on drugs, their physical, chemical, and physiological properties; he should be the consultant to the physician on therapeutic claims for drugs, their contra-indications and side effects; he should be able to evaluate as well as formulate dosage forms.

This is the ideal situation toward which we are striving and I believe that our curriculum is heading in that direction. But let me cite three recent observations without elaboration, that furnish a sober realization of the problems we face in achieving that ideal.

The first is a statement made by a prominent physician, a specialist in internal medicine and very friendly to pharmacy, in an appearance before the senior class in my College. When asked what professional service he expects from the pharmacist, his reply was that he expects to be furnished information on the availability, the types of dosage forms, the package size, and the price of medication, nothing more.

The second is a statement made before a pharmaceutical group by a high official in one of our leading pharmaceutical manufacturing companies in his discussion of the virtues of brand name drugs. In describing the apparent difficulties involved in prescribing generically an ointment containing an anti-infective in a non-irritating, non-allergic cream base, he mentioned that the pharmacist would

have to take the time and patience in his busy pharmacy to determine which of the available prefabricated products would meet these requirements, and this "might lead inadvertently to the selection of a product not quite so suitable to the patient", or that, "without instructions to the contrary, the pharmacist might justifiably compound the prescription extemporaneously, which may or may not be suitable for the patient".

The third is the sentiment expressed by one of the outstanding seniors in my College which may reflect the views of his counterparts in many of our colleges of pharmacy. When asked to give his written comments on and evaluation of the curriculum he stated, in essence, that he would be inclined to favor the "trade school" type of pharmaceutical education over the modern curriculum; that he has no desire to prepare a more palatable cough syrup when there are so many good ones already available from the manufacturer.

I mention these three observations to illustrate that it is the commodity concept, rather than the service concept, that appears to be dominant in pharmaceutical practice today. How does this relate to our curriculum, to what we teach, and to how we teach? As teachers we must realize that our task is only half completed when we have set up our curriculum and have developed the best possible syllabi and methods of instruction for the various courses. If our efforts are to have the dynamic effects on the practice of pharmacy that we hope for, we must establish and maintain constant, effective, and persuasive communication with the many publics with which we must deal—students, alumni, pharmacist-employers, manufacturers, and physicians. It is only through our good influence on the environments of these publics that we can hope to see the results of our teaching efforts achieve fruition.

Please forgive me if I appear to have gone off on a tangent. If you believe that I have, then you will agree all the more with my earlier suggestion that deans should be kept off the program.

SCOPE—OBJECTIVES—ORGANIZATION OF THE SEMINAR

A. P. LEMBERGER

Now that you have been properly welcomed to the seminar and to our campus, I would like to spend a short time in drawing your attention to the scope, objectives, and organization of our seminar. Since this apparently is the usual thing at these seminars, the committee felt we should at least start according to protocol. Although this is said "tongue-in-cheek," there is indeed a real value to be achieved by orienting ourselves to the tasks before us.

In planning this seminar, the committee recognized certain unique circumstances. Consequently, the program embodies something of a departure from past conferences of this group. As a result, it is all the more important that we embark upon the program geared to its objectives and attuned to its philosophy. Let me briefly review the development of the program and the deliberations of the committee in order to bring you this feeling for the seminar.

The Seminar Committee met to plan this meeting in January. It was apparent to the committee that in planning this meeting recognition had to be made of two important factors. These were the realization that the five year program of study was now a reality and that in the future the teachers of pharmacy would be meeting in general sessions every third year.

Because we are into our new program, the committee felt that any discussion of courses, per se, relative to the new curriculum would not be of real value because our curricula, course wise, have already been adopted. Thus, it seemed to us that a discussion of the merits of including courses such as physical pharmacy, manufacturing pharmacy, etc. in the curriculum and their proposed content would be similar to locking the barn after the horse has run off. However, the results of the survey issued by Dean Hewitt indicated a definite interest in course content on the part of the teachers of pharmacy. Therefore, if we were to fulfill this expressed interest, a different approach had to be found.

If we were to seek another approach to the consideration of course content other than by specific course titles, we recognized it would also mean that we would be forced to omit certain areas of the pharmacy curriculum from direct consideration at this seminar. We reached this decision, not without misgivings, in the realization and hope that if this seminar were to accomplish the primary objective set, some limit had to be placed upon its scope. Thus, as you observe from the title of the seminar, we have limited our deliberations to the technical pharmacy courses.

Well, what of this new approach? What is it? What are we going to do? Let me return to this in a few moments.

The new schedule of conferences calling for general sessions every third year also influenced our thinking. Let me explain. The second interest expressed by the teachers of pharmacy in response to Dean Hewitt's questionnaire was in the realm of methodology. Although not as great an interest was expressed in this area, it was significant and merited consideration. Thus, some thought was given to inclusion of topics pertinent to methodology. On the other hand, aware of the changing pattern in the schedule of meetings, it occurred to the committee that

teaching methods are important to all teachers in schools of pharmacy regardless of their area of specialty and that ample coverage of teaching techniques could probably be attained through the more frequent general sessions. And so we turned our attention to introducing a broader concept of the objectives recommended by the pharmaceutical survey for these seminars ". . . to come into fruitful contact and to keep pace with progressive content and methods of pharmaceutical teaching."

We have broadened the concept of "progressive content" to include subject matter itself and decided to devote a significant part of this seminar to symposia designed to bring to us the latest concepts and thinking in selected areas pertinent to the teaching of pharmacy.

Before returning to our approach or, if you will, the organization and specific objectives of the seminar, let me speak briefly of the philosophy we hope will pervade the seminar. You will note that in my discussion so far I have used the terms "we" and "our" when specifically referring to the actions of the seminar committee. If you will recognize that the committee functioned only as a designated portion of the membership of this seminar, then the "we's" and "our's" become enlarged to include all of us. This, then, is the basic philosophy we want for this seminar. Each and every one of us should feel a personal identification with every topic and every activity of this meeting.

If we do this it becomes unnecessary for me to remind you that this or any other seminar is only as valuable to the individual as is the extent of the individual's participation. If our workshops are to be of significance, if there is to be anything for us to take from this seminar, we must all first give something to be shared. If we don't do this, then it is as impossible for us to leave Madison this week-end with the knowledge we are taking something home with us as it is to pour milk from a pitcher before it is filled. Thus, active participation is not asked of you; it is expected.

Now let us return to a consideration of the approach we wish to make in this seminar to a useful and significant discussion of course content and subject matter. Bearing in mind that the scope is limited to technical areas, let's look at the specific objectives and organization of the seminar.

The first specific objective is to produce a syllabus for technical pharmacy instruction, not as a course by course progression, but as an overall sequence of topics to be mastered by the pharmacy student as he proceeds from the beginning to the conclusion of his work in pharmacy. I think we all agree that this is rather ambitious, an objective not likely to be reached in a one week seminar. But it should serve as the goal to guide us so that we don't get lost in the labyrinths of semantics and course titles. More likely as we look back upon this week we will see that we discussed a number of subject areas, that as a result of these discussions we have reevaluated some of our original thinking in regard to the relative importance of certain topics which we teach and that we have revised our approach, stressing certain topics a little more, deleting or de-emphasizing others and, in general, improving our courses. This can only come about, however, through frank expression of viewpoints and open-minded consideration of supporting arguments.

As I have indicated before, the extent of our penetration along the path toward the lofty objective cited depends in a large measure upon our ability to stay within the intended framework of discussion. If I may express a personal

opinion here, I would like to point out that it seems to me, even in my relatively short experience as a teacher, that we have considered at length both formally and informally the overall organization of the curriculum. I refer to discussions on such questions as: should physical chemical principles be taught as a separate course or integrated with technology?; should isotonic solutions be covered in technology or dispensing?; etc. To my knowledge general agreement has never been reached and, in my opinion, little more can be accomplished by continued discussion along these lines.

Thus the concept to be borne in mind during this seminar is that our primary interest is in the topics to be included in our technical preparation of the student and in the depth to which these should be pursued. To whatever extent possible we should try to avoid discussion of the organizational pattern to be followed in devising our individual curricula. As a framework of reference we have arbitrarily divided the sequence of instruction in pharmacy into four phases, which for lack of a better designation we are calling the first, second, third, and fourth course. It is critical to the success of the discussion that we keep in mind that these courses represent stages of development. Thus, in the actual curriculum each stage may involve several courses or may only be part of a larger course. To identify these specific courses is not in any way an objective of this meeting; our objective is to consider only the subject to be included in the respective stages of development and the relative emphasis to be placd on each.

It was the feeling of the committee that in this way all schools and all teachers of pharmacy could contribute in a positive way to the program. This approach should minimize differences which would otherwise arise due to factors such as curriculum sequence (2–3, 1–4, etc.) differences in teaching philosophy such as separation or integration of physical-chemical principles and differences in viewpoint regarding placement of subject matter in the chronological sequence of instruction of the student.

Organizationally, we have devoted the early sessions of the seminar to consideration of the curriculum. A syllabus for each of the four areas of instruction will be presented today and will serve as the starting point for our workshops. Four periods following the formal presentations of syllabi have been arranged to permit each of us to participate in a preliminary discussion of course content in each stage of instruction. Incidentally, we ask your cooperation in electing the workshop section you attend so that we split fairly evenly. Discussion will be fostered in smaller groups and so we hope that each section will number approximately 35–40 seminarians. During the mid-portion of the week we hope you continue discussing these matters informally so that on Friday morning, at the real working sessions, progress will be made in the direction of general agreement over course content.

On Friday morning, a three hour block has been set aside for a workshop in depth on each of the four subdivisions of the technical pharmacy curriculum. At this time, each seminarian is expected to choose that stage in which his major interest lies and participate in the full discussion. I am sure most of us feel some interest in more than one of these stages, but the committee felt that if any progress were to be made, we must break up into smaller groups.

I think it is readily apparent that if this phase of the seminar is to be successful, active participation is imperative and cooperation within the scope and objectives cited is mandatory.

The second specific objective of the seminar, as visualized by the committee, is that of personal professional advancement. It is the intention to provide the teacher with an opportunity for critical review and searching inquiry into certain selected areas of subject matter. We hope the seminarians feel challenged by the presentations and experience professional gain in terms of applicability to their teaching and research programs.

Topics selected for this series of symposia beginning Tuesday evening and running through Thursday are drug stability, solutions, disperse systems, sustained release, and ointments. These were selected on the basis that pertinent references to these areas are made in each stage of the pharmacy curriculum; thus, all teachers will find matters of direct application as well as gaining a broader personal insight into each of these topics.

In devising the program, we have allowed for a twenty minute discussion period following each paper, thus permitting further clarification and exploration of the topic under consideration. It was the feeling of the committee that this type of program, were it to show itself valuable, would provide a fruitful approach to future seminar programming, particularly in view of the changing pattern of the meetings.

This, then, is the overview of our seminar program. In five short days we will know how successful the meeting has been. As I have stated before, the key lies in the participation of the seminarians in the activities of the seminar and in our ability to accept and maintain the original intent of the discussions and symposia. I am sure you are as anxious as I am to begin the workings of this seminar.

SYLLABUS FOR INSTRUCTION IN PHARMACY

PHARMACY INSTRUCTION—PAST AND FUTURE

V. N. BHATIA

It is a difficult task to talk on a subject as general and as broad as the one assigned to me, to a group which has come here prepared to listen to discussions on very specific topics. It is also difficult to talk on this subject because I am sure that most of you have very definite opinions about it. I think it is important, however, that a group of teachers of pharmacy examine some aspects of the past and future of pharmacy instruction, because in all our deliberations, whether they be related to curriculum planning or technical subjects, we must not lose sight of our basic purpose for being here—and that is to help ourselves do a better job of teaching pharmacy in the years to come. It is not my intention to indulge in a discourse on the history of pharmaceutical education or to make predictions about the future; rather, I intend to point out what has been our role in the total spectrum of American pharmacy, and to indicate where I think we have some shortcomings which must be taken into account as we plan for the future.

In the total picture of American pharmacy, the role of the pharmaceutical educator is a very unusual one. We, and our predecessors, have had more opportunities to influence the development of pharmacy than any other comparable group in the world. Our work, our ideas, and most important, our concept of what the academic training of a pharmacist should constitute, has not been subject to direct control by any other pharmaceutical group. The pharmaceutical curriculum does not reflect the thinking of practicing pharmacists; rather, it represents our thinking. Indeed, we can be proud of our influence in the molding and evolution of the pharmaceutical profession.

Sometimes, though, we tend to forget where we fit in the evolutionary pattern of pharmacy. Kremers and Urdang, in their book, have pointed out that "to a great extent nonprofessional medicine was responsible for the development of American pharmacy as an independent calling, the professional aspects being incidental." One of the most important forces in providing the stimulus for the development of the professional aspects has been the leadership provided by the pharmaceutical educators. Because of our independent position, we have been able to set educational standards which have gradually elevated the scientific level of the profession; and we have been able to do so despite the chronic complaints about stringent educational requirements.

Unfortunately, pharmaceutical educators have never been completely united in accepting the responsibility for supporting the increasing educational requirements, or in accepting their role of leadership. From time to time when it becomes apparent that another important change or improvement in the curriculum is necessary to keep up with advancing knowledge, we can find some persons dragging their feet. Often they do so for fear that a more rigorous educational pattern may cause a drop in enrollment; or they might incur the wrath of some

local practitioners who fear some imaginary possibility of shortage in the supply of new pharmacists.

A recent case in point is the development of the course in physical pharmacy. The 1949 Seminar was responsible for really making us aware of this area and its importance. Almost everyone agreed about the value of such a course; but after twelve years, the adoption of the course in the curriculum is far from universal. In the colleges where such a course has been adopted, the content varies from meaningful to indifferent. At any meeting of pharmaceutical educators you can count on at least half a dozen persons saying "I am not sure that I understand what physical pharmacy is." One begins to wonder if they really want to know.

The important thing, however, is that pharmaceutical education has continued to progress and provide the leadership despite cries of anguish from those outside its ranks who lacked vision, and those within it who were timid. The signs of progess are many, the most recent advance being the increased reliance on the basic sciences as prerequisites for the professional courses.

It must, however, be pointed out that in this regard the teachers of pharmaceutical chemistry can point to their phase of the curriculum with much greater pride than we teachers of pharmacy. In recent years we, that is, the teachers of pharmacy, seem to have become most reluctant to accept change. The reasons for this are many. One may be that some of the changes in what constitutes pharmacy today are so drastic that some of us are not too sure of ourselves when we handle this new body of knowledge, and our response sometimes is to resist this change rather than put out the effort to bring ourselves up to date.

Another reason may be that because of our own training and past experiences we have become very attached to some of the so-called "art" of pharmacy and hate to give it up. This was very well expressed by Dean Webster at the Teachers' Seminar in 1960. Dean Webster pointed out "production of an elegant preparation by the exercise of an art has an attraction to both the teacher and the pupil. To forego this pleasant exercise, even though the elegant preparation is so seldom used as to be almost useless, requires a great deal of discipline. To give it up for a series of studies on surface tension or particle size seems almost a denial of the art." I do not mean to imply that the traditional "art" is always incompatible with scientific advances. What is unfortunate is the attempt to keep alive the archaic at the cost of the modern.

One can almost divide teachers of pharmacy into three groups. First, those who have had the foresight and the courage to modify their courses and to provide them with proper prerequisites in the basic sciences. These, unfortunately, constitute a minority. Second, those who continue to teach as though nothing has changed; they continue to teach the course in principles and processes of pharmacy in the same old way, regardless of the extended curriculum and of the increased preparation of the students who have to take their course. They continue to offer dispensing courses which qualify students to practice pharmacy 30 years ago. These, fortunately, also constitute a minority. Third, is the large group of us who, while recognizing the need for change, seem to be able to break the ties to the old pattern only half way. This group believes that physical pharmacy should be taught and teaches it. Unfortunately, the belief is not strong enough to advocate even a 4 semester-hour course in elementary physical chemistry as a prerequisite. So, they continue to spend most of their time teaching basic physical

chemistry in the physical pharmacy course and have very little time left to discuss the applications of the basic science to pharmacy. The result is that the students often fail to grasp the significance of the course. They cannot defend their offering the courses in pharmaceutical preparations prior to a course in physical pharmacy as a sound educational practice, but have learned to rationalize it in a variety of ways. For example, "the need for giving students some pharmacy early in the curriculum." Their courses in dispensing have been modernized, but their ideas again are mutilated by a lack of real conviction.

We teachers of pharmacy must do more than we have done so far if pharmacy is to remain the capstone of the pharmaceutical curriculum. Our courses must be made more challenging. The extended curriculum and our efforts for recruitment of students have resulted in an improvement in the quality of students entering the colleges of pharmacy. If these students are faced by antiquated courses in the most important portion of the curriculum, they will feel shortchanged. This, then constitutes one of the most important challenges facing us in the immediate future. Our task of preparing for the future can be carried out easily, however, if we keep four things in mind.

First, we must remember that strengthening of the curriculum in the past has never hurt pharmacy, but has always helped it—even in such matters as enrollment. In this regard I cannot help but make the obvious statement that the work of planning for the future would be so much easier if all of us knew and understood what has gone on in the past. I have often felt that such books and reports as *The Pharmaceutical Curriculum* by Blauch and Webster, the *Report of the Pharmaceutical Survey,* and even old volumes of the *American Journal of Pharmaceutical Education* should be required reading for all new teachers in colleges of pharmacy.

Second, we must not become discouraged by the fact that all of pharmacy does not immediately embrace and use what we teach. One must remember that in some parts of the country only a little more than half of the pharmacists practicing today have had the benefit of a four year pharmacy course, and so it will be a long time before we see the full effects of even the four year course on the practice of pharmacy.

Third, although there have been many improvements in recent years, undergraduate pharmaceutical education must be better financed. This is necessary to bring about the changes and the improvements that will be required in the future. Part of the responsibility here belongs to all of us educators as well as to the administrators. We have not been able to convince those who control the purse strings of our importance, our role and our need for more financial support to provide the kind of professional education that we must. We have all seen instances when curricular and other improvements have not been possible because of the cost involved. While realizing that educational institutions do not have unlimited budgets, one has a right and duty to be critical when one sees curricula with serious gaps which are not remedied because of the failure to secure adequate financial support. Six years ago, at the last Pharmacy Teachers' Seminar in Indianapolis, there were many among us who, while acknowledging the value of a course in manufacturing pharmacy, could not see how they could ever offer it because of the cost involved. It reminded me of an editorial by the late Dean Lyman which I ran across while reading some old volumes of the *American Journal of Pharmaceutical Education.* The editorial was written in 1938, and he was chastizing the Syllabus Committee for its failure to include a

certain course in its recommendations. The reason for not including the course was that some colleges might find it too expensive to teach. Dean Lyman labelled this a "pathetic calamity" and went on to say in his inimitable style "when a school reaches that point it better give up courses in pharmaceutical sciences and devote its efforts to teaching elementary bookkeeping and penmanship."

Fourth, we must be aware of the fact that a much broader background of scientific knowledge will be expected of those who teach pharmacy in the years to come. It should be recognized that modern treatment of the subject matter of pharmacy and the better quality and preparation of the students in the five year course makes it necessary for us to have the proper understanding of physical, organic and biochemistry in order to be truly successful teachers. We cannot continue to think of these basic sciences as being only in the province of the pharmaceutical chemists. Actually, I believe we have made a great deal of progress in this direction and the days are long past when graduate work in pharmacy was less rigorous than in other pharmaceutical sciences.

These, then, are some of the thoughts that motivated your Seminar committee at arriving at the new format for this teachers' seminar. This Seminar is divided into two parts, the part devoted to curriculum planning and the part dealing with technical topics. As we enter into the task of educating students in the five-year course, it is fitting that we examine and discuss both the arrangement of the courses and get some idea of the modern topics that might form the contents of these courses. I would like to emphasize that your committee felt that the only way we could get the most out of the curriculum part of the program was to approach the discussions as free of bias as possible. That is, we must not think of the first, second, third and fourth courses in terms of old titles, such as "preparations" or "technology," but as four levels of achievement in learning of the body of knowledge we call pharmacy. Only then will we arrive at new and stimulating ideas and not get bogged down in the same old arguments that reappear every year.

In conclusion may I point out that although I have mentioned several of our shortcomings, I am conscious of the fact that actually our achievements probably outweigh them. Perhaps I can illustrate my point of view and intent by a story I was told by Dr. Melvin Gibson, my colleague at Washington State University. Once, after Dr. Gibson had written a particularly controversial editorial in our *Journal*, he received a letter from Dean Lyman which said "You are keeping the Indians stirred up and that is progress." In this instance I hope that the inverse is true and that this Indian has done some stirring of you.

THE FIRST COURSE IN PHARMACY

INTRODUCTION TO PHARMACY AND PHARMACEUTICAL SYSTEMS

D. M. SKAUEN

In the text, *The Pharmaceutical Curriculum* by Blauch and Webster, it was recommended that the first course in pharmacy should be Pharmaceutical Preparations. Since the title Pharmaceutical Preparations has various meanings, the text further states the objectives and a suggested course content.

The objectives as outlined are: "1. understanding of the principles and processes of preparing pharmaceuticals and familiarity with the various classes of pharmaceuticals as such and as they are distinguished from one another; 2. mastery of the essential skills used in preparing standard pharmaceuticals; 3. understanding of the preservation and storage of specific types of pharmaceuticals; 4. information with regard to the general therapeutic usefulness and the dosage of the various pharmaceuticals."

These objectives have been met in a variety of ways. Two methods, however, have been adopted most frequently. At one extreme, more than half of the schools surveyed (13 of 22) are teaching or intend to teach a beginning course emphasizing types of preparations and their manufacture.

At the opposite extreme, a sizeable number of schools favor a program in which the types of preparations, their manufacture and technology are interwoven with other courses, such as physical pharmacy or pharmaceutical technology.

Proponents of both approaches argue vehemently about the advantages for their particular method and the disadvantages of other methods.

Individuals who teach a specialized course in Pharmaceutical Preparations claim that since this is the first course in Pharmacy, much of the material, although elementary, is basic to an understanding of future courses. It is necessary, therefore, to learn the art of pharmacy, to learn to manipulate equipment, and to acquire skills in preparing pharmaceutical products. Emphasis should be upon technics and skills rather than on theory. The student under this system will become familiar with dosage forms and will gain the insight to recognize differences and similarities among classes. As he acquires skills he prepares more difficult products; as his knowledge increases he studies more complex classes of preparations.

Advocates of this method of presentation feel that the student will be able to profit more fully from the theoretical and physical pharmacy courses to follow since he will be thoroughly grounded in the fundamental classes of preparations.

Proponents of the integrated system prefer to explain classes of pharmaceuticals under their proper physical or chemical class. For example, liniments might be discussed as a solution under the subclass of non-aqueous solutions.

It is also considered feasible to discuss syrups under the heading of specific gravity or viscosity and aromatic waters under filtration or solutions.

The supposition employed in this regard is that Pharmacy has become a science rather than an art, and emphasis should be placed on the physical and chemical principles underlying pharmacy rather than placing emphasis on skills and manipulations.

The objective of this seminar is to try to suggest *what* to teach in contrast with how or when it is to be taught. For the purpose of our deliberations this week it makes little difference perhaps, whether Soft Soap Liniment is discussed under Liniments, Solutions, Non-aqueous Systems, Viscosity, or Filtration as long as the student knows what we want him to know about the subject.

Accordingly, I am outlining in a way familiar to us all those topics which I feel ought to be considered in the first course in pharmacy. This syllabus outline should be considered mainly as a base of operations, to be analyzed, reconstructed, and revised during the next few days.

Syllabus for The First Course in Pharmacy

1. Introduction
   a. Objectives
   b. Scope
   c. General principles
2. Waters
   a. Definition
   b. Methods of preparation
      Distillation
      Solution
      Alternate Solution
   c. Fundamentals of filtration
      Filtering media
      Filter papers
   d. Storage and Preservation
   e. Examples and Uses
   f. Laboratory manufacture of two or three examples.
3. Syrups
   a. Definition
   b. Methods of Preparation
      Percolation
      Simple solution with heat
      Simple solution without heat
   c. Problems associated with sugar in aqueous systems
   d. Preservation problems
   e. Discussion of unusual types
   f. Uses
   g. Laboratory preparation of three syrups

4. Solutions
   a. Definition(s)
   b. Preparation
      Solution
      Chemical Reaction
      Sterilization
      Extraction
   c. Reasons for each method
   d. Unusual types
   e. Reactions if present
   f. Uses
   g. Laboratory work including each manufacturing method

5. Infusions and Decoctions
   a. Definition
   b. Method of manufacture
   c. Uses

6. Mucilages
   a. Definition
   b. Methods of manufacture
   c. Types of mucilages
   d. Viscosity characteristics
   e. Structural properties
   f. Uses
   g. Manufacture of one or two varieties

7. Glycerites
   a. Definition
   b. Manufacturing methods
   c. Unusual heating requirements
      Methods of obtaining above
   d. Stability characteristics
   e. Chemical reactions
   f. Applications and uses
   g. Laboratory manufacture of one example

8. Mixtures and Suspensions
   a. Definition
   b. Preparation
   c. Properties
   d. Methods to improve quality
      Stabilizing technics
      Formulation
   e. Unusual Examples
   f. Laboratory manufacture of two of three examples

9. Magmas, Gels and Jellies
   a. Definitions
   b. Similarities and Differences
   c. Examples
   d. Properties
   e. Stabilization
   f. Preparation of one example of each type in the laboratory

10. Emulsions
   a. Definition
      General
      Official
   b. Reasons for Emulsification
   c. Composition
      Oil phase
      Aqueous phase
      Emulsifying agents
        Properties
      Classification
        Examples
   d. Methods of Preparation
      Equipment
      Bottle method
      English method
      Continental method
   e. Preservation
      Creaming
      Flocculation
      Breaking
   f. Official examples
   g. Laboratory preparation of one emulsion by each method.

11. Lotions
   a. Definition
   b. Types
      Solution
      Suspension
      Emulsion
   c. Examples
   d. Methods of preparation
   e. Laboratory preparation of two or three

12. Liniments
   a. Definition
   b. Types
      Alcoholic
      Oily
      Emulsion and suspension
   c. Preparation technics
   d. Examples
   e. Laboratory manufacture of two

13. Ointments
    a. Definition
    b. Classifications
        According to penetration
        By composition
        Chemical
    c. Types of bases
    d. Types of ointments
    e. Methods of preparation
        Fusion
        Levigation
        Milling
    f. Packaging
    g. Stability characteristics
    h. Official Ointments
    i. Laboratory manufacture of six to eight by various methods and illustrating various types

14. Pastes, Cerates, Plasters
    a. Definitions
    b. Preparations
    c. Similarities to and differences from ointments
    d. Examples
    e. Laboratory preparation of one paste

15. Suppositories
    a. Definition
    b. Brief comments on rectal absorption
    c. Types of suppositories
    d. Bases
        Limitations and advantages of each
        Properties
        Problems
    e. Manufacturing technics
        Hand
        Fusion
        Compression
    f. Laboratory work of sufficient duration to insure familiarity with bases and the three methods of manufacture—about six sets of suppositories

16. Spirits
    a. Definition
    b. Manufacturing methods
        Problems to consider
            Filtration
            High alcoholic content
    c. Examples
    d. Preservation problems
    e. Laboratory preparation of two spirits

17. Elixirs
    a. Definition
    b. Composition
    c. Manufacture
        Difficulties associated with
            Viscosity
            Clarity
            Volatility
    d. Examples
    e. Preparation in the laboratory of three examples

18. Tinctures
    a. Definition
    b. Preparation
        Percolation
        Maceration
        Solution
        Solution and chemical reaction
    c. Discussion of extraction problems
    d. Examples
    e. Laboratory preparation of one example by each method

19. Fluidextracts
    a. Definition
    b. Preparation
        A thru E
        Reasons for each type
    c. Examples

20. Extracts
    a. Definition
    b. Comparison with Fluidextracts, Tinctures, Infusions and Decoctions
    c. Preparation
    d. Examples

21. Powders
    a. Definitions
    b. Types
        Bulk
        Divided
    c. Manufacture
        Subdivision
        Mixing
        Sifting and screening
    d. Preparation of Divided Powders
        Kinds of paper
        Paper sizes
        Folding

Dividing powder
Weighing
Blocking and dividing
By eye
By measuring device

e. Special problems
f. Packaging
g. Examples
h. Laboratory manufacture of five or six preparations

22. Capsules
a. Definition
b. Advantages
c. Types
Hard, Soft, etc.
d. Storage
e. Preparation of filled capsules
Powder
Size
Filling methods
Cleaning
Packaging
f. Special problems
Liquids
Masses
Eutectic mixtures
Deliquescent substances
g. Laboratory manufacture of three or four preparations

23. Pills
a. Definition
b. Manufacture
Mixing
Forming mass
Dividing mass
Shaping
Finishing
Coating
c. Packaging
d. Special problems
e. Laboratory manufacture of two or three examples

24. Troches
a. Definition
b. Manufacture
c. Examples
d. Uses
e. Laboratory preparation of one example

25. Tablets
    a. Definition
    b. Popularity
    c. General Types
        Molded
        Compressed
        H.T., T.T., D.T., C.T., etc.
    d. Manufacturing methods
        Molded
            Standardization of mold
            Choice of excipient and base
            Molding
            Drying
            Packaging
    e. Compressed
        Weighing ingredients
        Mixing
        Granulating
        Compressing
    f. Examples
    g. Laboratory manufacture of four or five examples
26. Effervescent Salts
    a. Definition
    b. Manufacture
        Wet or fusion
        Granulation
        Drying
        Packaging
    c. Unusual types
    d. Laboratory preparation of one example

THE SPHERE OF KNOWLEDGE AND THE HELIX OF LEARNING: A CRITICAL EXAMINATION OF PHYSICAL PHARMACY

ALFRED N. MARTIN, JR.

"For science, however, no exclusive claim is here made: you are not urged to erect it into an idol. The inexorable advance of man's understanding in the path of knowledge, and those unquenchable claims of his moral and emotional nature, which the understanding can never satisfy, are here equally set forth. The world embraces not only a Newton, but a Shakespeare—not only a Boyle, but a Raphael—not only a Kant, but a Beethoven—not only a Darwin, but a Carlyle. Not in each of these, but all, is human nature whole."—JOHN TYNDALL.

Our teaching and the profession of pharmacy has gained immeasurable, although perhaps intangible, benefits from these yearly teachers' seminars. But, in order to realize the greatest good from such meetings, the participants must always guard against one difficulty. I am referring to the possibility of discussions continuing throughout the week without an initial clear recognition of agreement and disagreement. Each of us brings along his own set of experiences and viewpoints, and it is sometimes difficult to understand what others are driving at. In order to refrain from sowing such seeds of confusion at the outset, I will attempt to state clearly my interpretation of physical pharmacy, what I think should be included in this subject, where the course should be introduced into the curriculum, how I think it should be taught, and where and how physical chemical principles can be incorporated into other courses in the pharmaceutical sciences. You may wish to differ with me strongly on a number of points, and I urge you to do so. My main objective is not to seek complete agreement, but rather to present ideas in such a way that areas of agreement and difference are made quite apparent; we can then go on in later discussions to explore points of disagreement and come to some useful conclusions in the teaching of physical pharmacy.

I. The Sphere of Knowledge and Experience

Let us begin with a broad perspective of knowledge and education, then narrow down the view until we are focusing our attention on the areas of pharmacy and, finally, on the specific course content of physical pharmacy.

The Disciplines of Knowledge. Harold Cassidy, writing in the *American Scientist*, has diagnosed the problems of conflict and misunderstanding which exist between the sciences and the humanities (1). He suggests a prescription for treating the underlying causes and bringing about a cure of mutual misunderstanding and mistrust between scientists and humanists. In his discussion, he visualizes the intellectual structure of the university as a sphere with the arts and sciences as the equatorial belt, the philosophies at one pole, and the technologies at the other. A modified version of this sphere of knowledge is shown in Fig. 1. The various basic disciplines of knowledge are seen to circumscribe the sphere in clock-wise order from mathematics (considered by many as both science and art) through the physical, biological, and behavioral sciences to eco-

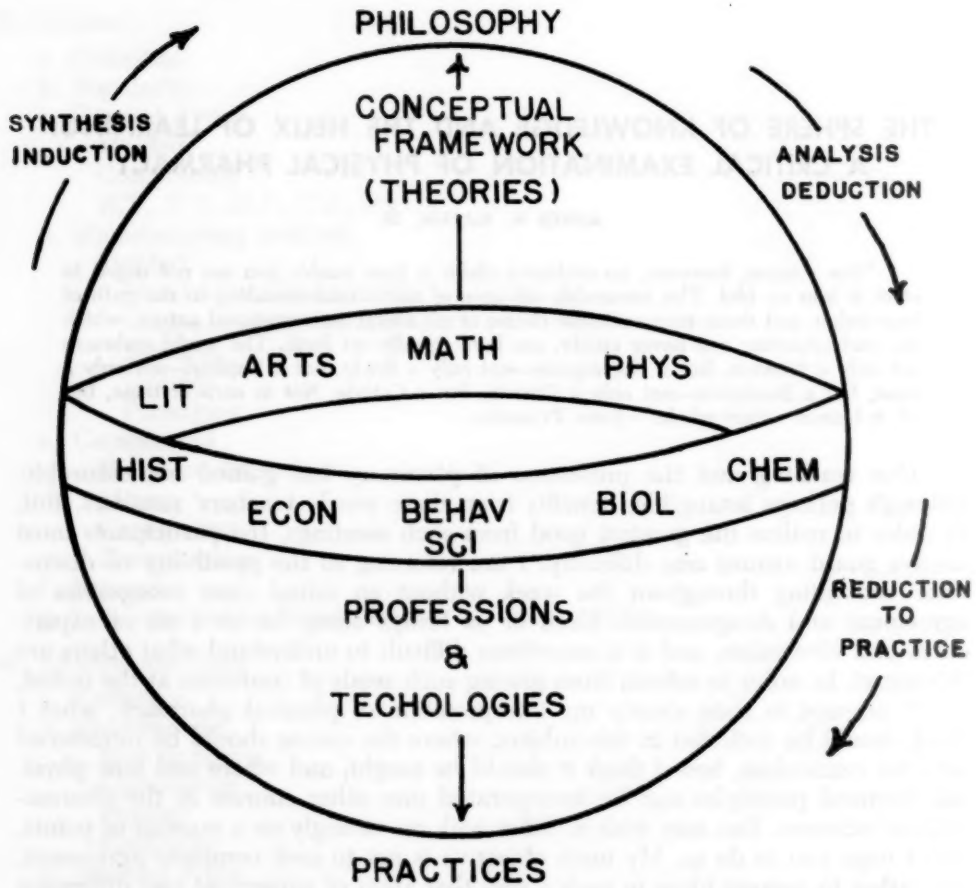

Figure 1.

nomics, history, literature and art. The basic arts and sciences contribute a body of knowledge in support of other areas of learning, namely the professions and technologies. Medical science, for example, depends primarily upon the biological, physical, and behavorial sciences, but it also receives a flow of knowledge and experience from the areas of economics, history, literature, and fine arts. At the base of the sphere we find the practices, trades, and crafts to which all knowledge must be reduced if we are to make useful application of our information and skills. Knowledge must also proceed through synthesis and generalization toward a conceptual framework and eventually to a limited number of philosophies where many of the fundamentals of knowledge can be united.

The figure is meant to show general relationships, and to suggest similarities and differences among the various areas of the sciences and humanities. It is not exhaustive in detail and is not meant to be taken too literally.

Areas of Specific Activities. Perhaps we can understand more clearly the organization of knowledge and its reduction to practice if we represent the various disciplines arranged around a circle depicting a cross-sectional cut through the sphere already shown. The reduction to practice is considered as forcusing inward toward the center of the circle, as shown in Fig. 2. The outer

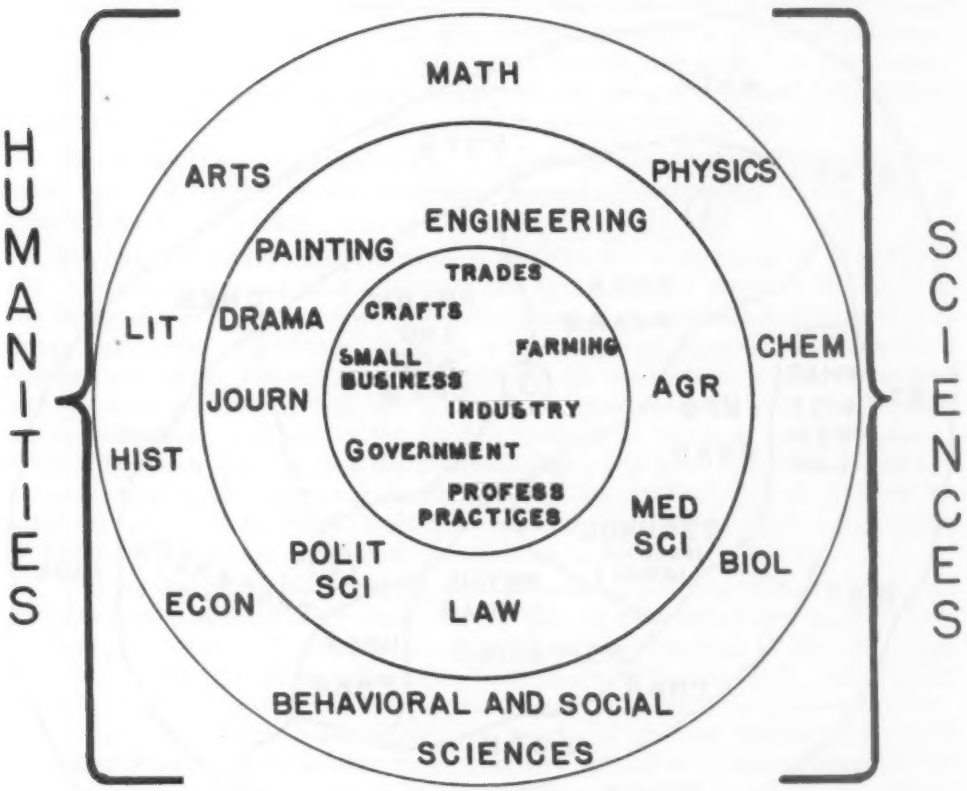

Figure 2.

band contains the basic disciplines, the next inner-most band contains the professions and technologies, and the central portion contains practices of industry, government, and small business. Although each profession and technology applies the knowledge of both the humanities and the sciences, it is generally found to emphasize one or several basic areas, as the specific arrangement around the circle is meant to suggest.

II. The Pharmaceutical Sciences

The pharmaceutical sciences constitute part of the area of the medical sciences shown in Fig. 2. This portion of the diagram is magnified in Fig. 3 so as to highlight the pharmaceutical areas and to show the basic sciences and humanities to which pharmacy is most closely related.

Definitions of Pharmacy and Physical Pharmacy. The definition of pharmacy, which emphasizes the collection, synthesis, preparation, and control of drugs and drug products, is found in standard texts and is well-known to all of us here. But the word "pharmacy" has two distinct meanings, and confusion sometimes arises through a failure to distinguish between the two.

In the broad or generic sense, pharmacy signifies the whole of the pharmaceutical sciences shown in Fig. 3; from manufacturing to medicinal chemistry, from pharmaceutical administration to pharmacology. In the specific sense, on the other hand, pharmacy encompasses the areas of general pharmacy, manu-

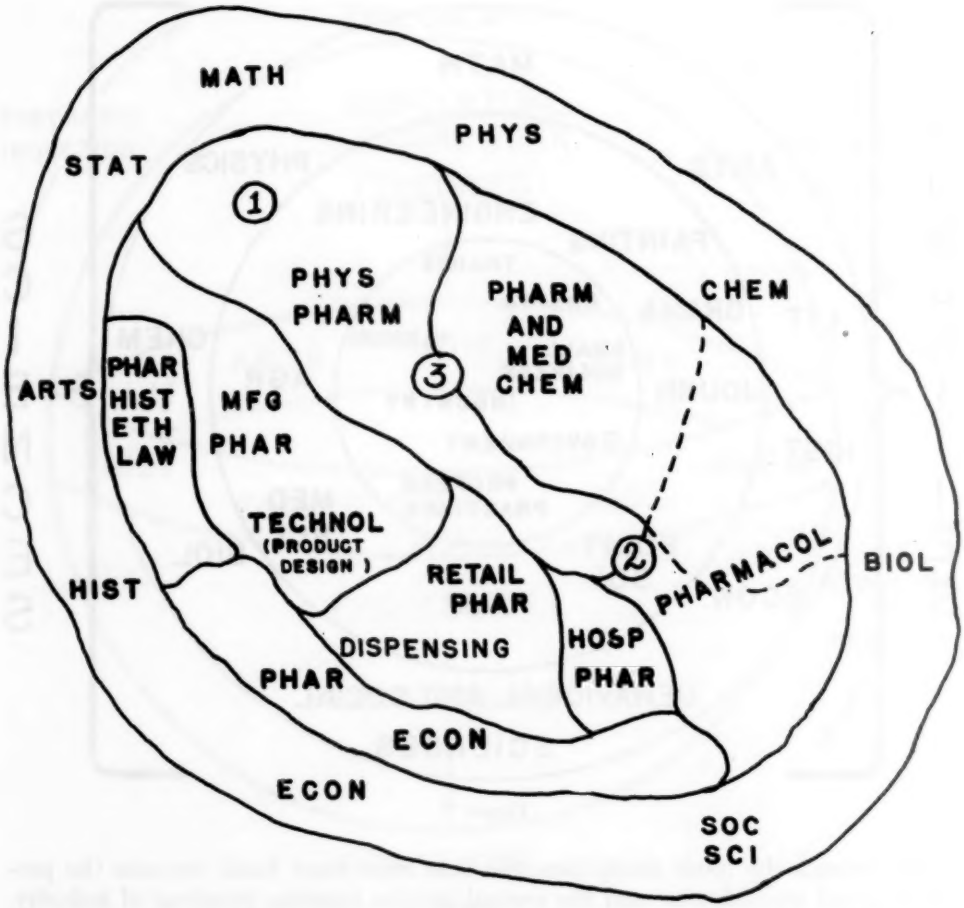

Figure 3.

facturing, drug compounding and dispensing, retail and hospital pharmacy, and forensic pharmacy.

The word "pharmacy" in the term physical pharmacy is used here in the broad generic sense, since physical pharmacy embodies the physical chemical principles of the various applied sciences of pharmacy. Physical chemical principles are applied not only to the design and preparation of dosage forms but also to the synthesis and analysis of drugs and a study of their distribution in the body and action at receptor sites. Terms such as biopharmaceutics (2) and chemobiodynamics (3) are appearing in recent literature as titles for these new areas of drug science.

The Scope of Physical Pharmacy. As seen in Fig. 3, physical pharmacy borders on the basic sciences of mathematics, physics and chemistry; and it involves fundamental aspects of drug design and manufacturing, compounding and dispensing in the areas of retail and hospital pharmacy, and the physical chemistry of biopharmaceutics in the areas of pharmacology and pharmaceutical chemistry.

Since it is concerned with the preparation of solutions, dispersions, and solid dosage forms, physical pharmacy is of considerable importance to retail,

hospital, and manufacturing pharmacy, and it has made most of its contributions in these areas in the past ten years. The beginning course in physical pharmacy usually stresses these aspects of pharmacy, although one finds that the student is also deeply interested in biopharmaceutics and drug action, and introductory material in these areas should be included in the beginning course.

The numeral *one* encircled in Fig. 3, signifies the basic area of physical pharmacy, and an outline of the beginning course corresponding to this area is attached as Appendix 1.

Physical pharmacy can also make a contribution to the area of pharmacology. In recent years we have witnessed the application of physical chemistry to the study of the biological absorption, distribution, metabolism and excretion of drugs, and to the uses of these findings in the design of controlled and sustained release medication. We can now look ahead to the time when the pharmacologist and physical pharmacist will use physical chemical methods in a joint assault on the refractory problem of the mode of action of drugs at receptor sites. I think it is safe to predict that the pharmacologist will soon find it a necessity to have a background in physical chemistry if he does not wish to look on from the sidelines while others make significant advances in the areas of drug action, biological distribution, and drug metabolism.

Toward this end of preparing the pharmacologist and the research and development pharmacist for their role in this rapidly advancing area, I have drawn up an outline of a course, Physical Chemical Principles in Pharmacology, which could be offered on an elective basis in the fifth year of the college curriculum. In perusing some of the pharmacy college bulletins, I observe that several schools have already anticipated this need and are now teaching courses in biological kinetics. I hope that those teachers present who are responsible for such courses can give us some information during the week about this interesting development in pharmacy. The encircled number *two* in Fig. 3 signifies the application of physical pharmacy to pharmacology, and corresponds to the outline of the proposed course, included as Appendix 2.

As symbolized by the encircled number *three* in the figure, physical pharmacy can also contribute to pharmaceutical and medicinal chemistry. At the 1958 Teachers' Seminar on Pharmaceutical Chemistry at the University of Minnesota, Dr. Chertkoff and I outlined an elective course in the applications of physical organic chemistry in the curriculum of the pharmaceutical sciences. The outline has been modified somewhat and appears in Appendix 3 as "Physical Chemical Principles in Pharmaceutical and Medicinal Chemistry."

I realize that the group here may be more interested in physical pharmacy as it applies to the sequence of courses in the area specifically called pharmacy. However, most of us would agree that physical pharmacy will not realize its full usefulness unless it is applied to chemical and pharmacological areas as well as preparative and manufacturing pharmacy. As we learn more about the structural features of drugs at receptor sites, together with the thermodynamics and kinetics of drug action, physical chemical principles should play an increasingly important role both in medicinal chemistry and pharmacology.

Consequently I visualize a modern pharmacy curriculum as containing three distinct courses involving the physical chemical aspects of medicinal agents and dosage forms: one course of six or eight credits on fundamental physical chemical principles and drug design (technology), and two additional (perhaps elec-

tive) courses of three credits each on the physical chemical aspects of pharmacology and pharmaceutical chemistry. The beginning physical pharmacy course can be taught in the third, fourth, or fifth year; the others are more advanced courses for the fifth year undergraduate or beginning graduate student. Prerequisites for the beginning physical pharmacy course include courses in beginning mathematics, physics, quantitative analysis, and organic chemistry. Calculus is highly desirable, but if not available as a prerequisite, it may be incorporated to a limited degree in the physical pharmacy course. I feel that physical chemistry is not required preliminary to these physical pharmacy courses, and I will elaborate on this later in the talk.

Modification vs. Mummification. Some of our colleagues have stated that one of the serious problems in pharmacy education today is the lack of agreement on the nature, scope, and content of physical pharmacy. Frankly, I hope that we will not try to allay the fears or to quiet the troubled minds of our critics by proposing a course so agreeable to all that it is accepted without modification into pharmacy curricula across the country. I am afraid that any such unanimity would spell mummification of the course. Physical pharmacy is today too much a field of challenge, change, and controversy to be looked upon in the same light for long by any two teachers.

Discussions still rage in chemical society meetings as to where and how to teach general chemistry, organic chemistry, and analytical chemistry. The subject matter in the textbooks in these fields has only recently been markedly revised from what is called the "classical approach" to these chemical subjects. This is an age of idol-breaking, let us not try at this meeting to mold a physical pharmacy idol to be worshipped by all its disciples in the years ahead. Discovery and modification are much more desirable than conformity and regulation at this stage of the development of physical pharmacy.

III. The Helix of Learning

Levels of Learning. The trend in college education today is toward the teaching of concepts, methods, and broad principles with the realization that they are equally as important as facts and techniques. But, before the student can apply the fundamental principles to the solution of problems, he must acquire a minimal body of facts. The beginning courses in basic science, mathematics, and pharmacy provide information together with a qualitative view of the conceptual framework that undergirds the various areas of knowledge.

Later courses, then, consolidate the sometimes disconnected pieces of information; and the upper-level courses should finally correlate the principles and facts in a quantitative way and apply them to the solution of practical problems.

This hierarchical organization of the curriculum from simple to more complex suggests the idea of a spiral or *helix of learning*. We can draw an analogy between the helical structure of many proteins, stabilized by the bridging effect of hydrogen bonds, and the spiral-like nature of the learning process in the various areas of our curriculum. Pauling and Corey have shown that some fibrous proteins consist of individual spirals, and these chains are then woven together to form 7-strand cables. Correspondingly, we may depict the pharmaceutical sciences as a 4-strand rope, constructed from the individual helices: pharmacy, the basic and applied physical sciences, chemical sciences, and the biological sciences. These four strands are schematically represented in Fig. 4.

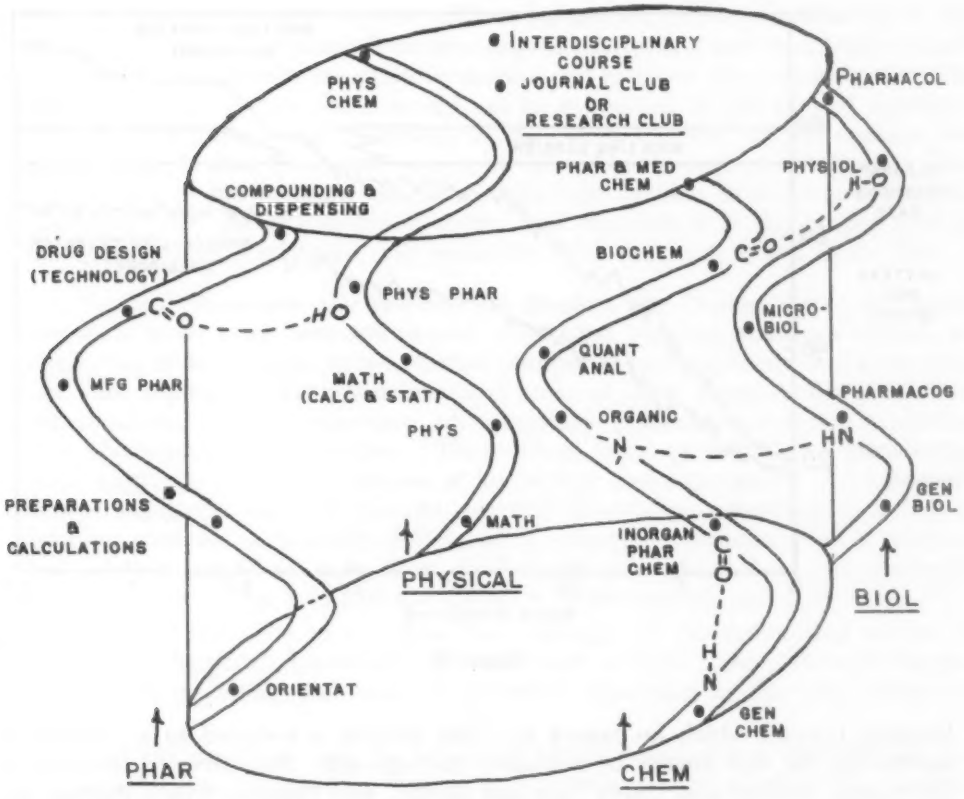

Figure 4.

Vertical intra-strand bridges (only one is shown) suggest correlation and "feedback" from one course to another in a single area, whereas horizontal inter-strand bridges are meant to signify interdisciplinary courses and proseminars which could be taught jointly by members of several departments.

We need not discuss each of the areas in turn shown in Fig. 4. The helical nature of learning is particularly evident in the strand of the physical sciences. I will use this sequence of courses to explore the idea further. But, before doing this, we must investigate the *learning curve* of the educational psychologist.

Will I Become a Main Line or Branch Line Operator? The educational psychologist tells us that learning in a new subject ordinarily begins slowly, then increases rapidly, and finally levels off at a limit of peak performance. But, this is a gross view of the learning process. If we investigate daily progress, we find peaks, valleys, and plateaus in acquisition of information and skills. In Fig. 5, I have plotted the combined results of several studies, made at the turn of the century, on the speed of learning to receive telegraphic code. Similar curves apply to the study of golf, music, and, no doubt, pharmacy and teaching as well. Aside from the almost daily "ups and downs" in the progress of the learner, we observe definite plateaus in the figure where learning is arrested temporarily. Finally, we see that the ordinary telegraph operator reaches a leveling-off in

Figure 5.

learning beyond which he cannot go. This student is resigned to a position of mediocrity; he will always be a branch line operator. The curve of learning of the second student also shows "ups and downs" and plateaus which indicate no progress. However, he is presumably more highly motivated to master the skill of telegraph receiving. He is stimulated to the point where, following a long plateau of no apparent progress, he is able to break through the "main line barrier" to reach his full potential of performance. This man will become the main line operator. Parenthetically, we might use this approach in asking our students, and ourselves as well, "Will we become main line or branch line pharmacists and teachers?"

The Helical Learning Curve Applied to Physical Chemical Studies. What we really want to do with this characteristic learning curve is to visualize it coiled into a helix of learning as shown in the previous figure (Fig. 4). A student advances, for example, in the physical chemical sciences, falls back occasionally, and then he reaches plateaus of negligible progress. But, if we establish the sequence of courses from the more descriptive and qualitative to the more rigorous and quantitative, then the strand constitutes a continuous logical series of *helical learning curves* which spiral always upward.

The pharmacy student acquires a number of physical chemical principles in his general physics and chemistry courses. He is reintroduced to some of these in new context at a higher plane of the helix, for example, the quantitative analysis course; only then is he prepared to launch into a course such as physical pharmacy. And, if he goes on to graduate school, he will take advanced courses in physical chemistry and mathematics. To use a metaphor of W. Mansfield Clark, we might say that the student is not prepared to venture into the choppy

seas of physical chemical studies without having learned his seamanship in the chartered waters of general chemistry, organic chemistry, and quantitative analysis (4). Consequently, we must be careful not to place physical pharmacy too early in the curriculum, for it would not be supported by the needed prerequisites. By labeling physical pharmacy as the "second course" at this seminar, we must not imply that it necessarily is to be offered in the second college year. The helical idea of the learning process should help us plan to undergird physical pharmacy with the proper prerequisites, and establish it at the proper turn of the spiral, which, incidently, will no doubt differ from one school to the next.

Physical Pharmacy; the Student, the Teacher, the Course. Up to this point, two main ideas have been introduced: *First*, that physical pharmacy obtains its wellspring of knowledge from a limited number of basic sciences, and it, in turn, can lend support to the pharmaceutical areas of drug design and manufacturing, retail and hospital pharmacy, pharmacology, pharmacognosy, and medicinal and pharmaceutical chemistry. (These ideas were presented by introducing what might be called the "sphere of knowledge and experience" (1).) *Second*, it was suggested that the student acquires knowledge according to a helical learning process, occasionally falling back, sometimes remaining on a plateau, but, always acquiring new facts, techniques and principles, and gradually assaulting the higher levels of the spiral of understanding and abstraction.

I would now like to use these two concepts in the concluding section to summarize the points I have already made and to make some additional suggestions for introducing and teaching physical pharmacy in the pharmaceutical sciences.

Physical pharmacy will be less than highly successful if included as part of the beginning preparations course. It is incongruous to combine the teaching of colligative properties, ionic equilibria, and quantitative aspects of solubility phenomena with the names, methods of preparation, and uses of waters, syrups, solutions, and spirits. The kinds of information involved here are sufficiently different to warrant separate courses, and in the interest of the student should be taught as such. Marcus has already reported on the difficulties involved in combining physical pharmacy and pharmaceutical preparations (5).

This does not mean that physical chemical principles should not be a part of the beginning courses in pharmacy. Principles such as emulsification, solvent application, subdivision of drugs, extraction, and clarification are being taught effectively at several levels. But, rather than attempt to precede all courses that use such principles with a low-level course in physical pharmacy, we should attempt to devise ways of effectively introducing these concepts in a graded manner into the courses of the curricular helix. Care must be taken not to cause unnecessary duplication nor oversight of important topics. Then, at the proper level, following courses in mathematics, physics, organic chemistry, and quantitative analysis, the beginning physical pharmacy course may be introduced.

Many students, particularly those in pharmacy and related medical and biological sciences, are confused and discouraged by the abstract concepts of a physical chemistry course early in the curriculum. Accordingly, I do not recommend physical chemistry as a prerequisite for physical pharmacy. The physical chemical principles needed by the undergraduate student can be adequately taught in the physical pharmacy course. Some may choose to offer elementary physical chemistry instead of physical pharmacy, but I do not believe that both

courses are needed. I like to teach physical pharmacy as a two-semester course with the inclusion in the second semester of considerable material known today as pharmaceutical technology (drug product design). Students intending to enter graduate school should then take a standard two-semester course in physical chemistry, preceded by the necessary mathematics courses.

For the student in the research option of the pharmaceutical curriculum (and for the student in the professional option, if possible) I would highly recommend a course in calculus and statistics, as suggested by Blauch and Webster (6). Today, calculus and statistics are not just working tools for the researcher, but are truly cultural in nature. The student who has had some training in statistics can make more intelligent decisions in business and science and can make better judgments in his daily contacts with others. In his reading in biology, psychology, or sociology, as well as in the physical sciences, he will constantly be confronted by the magic integral sign of the calculus. Any intelligent young person today should have an acquaintance with some of these basic concepts of mathematics. Therefore I would recommend an introductory course in calculus and statistics for its general cultural worth as well as for its specific utility in organizing and expressing scientific data and laws. If such a course is not provided, a limited amount of calculus and statistics can be incorporated in the course in physical pharmacy as suggested by Higuchi (7).

I am in disagreement with those who maintain that all of pharmacy is physical pharmacy and that no additional teacher in physical pharmacy is required. This is a mistake, for unless someone on the staff specializes in physical chemistry as applied to the pharmaceutical sciences, there is the likelihood that no one will take the responsibility. Although all schools may not find it desirable to establish a separate department of physical pharmacy, at least one member of the staff should teach and/or do research in this area. In addition to being responsible for the courses in physical pharmacy, he can be of assistance to the teachers in other areas in planning the incorporation of physical chemical principles at various levels throughout the curriculum. And, he can be called upon to present special lectures in pharmacy, pharmacology, and medicinal chemistry if the professors in charge of the various courses desire a talk on some physical chemical topic.

Finally, I would like to suggest that we consider a course in the final year of the curriculum, designed to tie together the knowledge acquired in the separate helix strands of Fig. 4. At the top of the sketch I have indicated that some such critical survey, journal club, or research seminar might be used to integrate and unify the student's knowledge. For some time now, the course in compounding and dispensing has been referred to as the capstone of the pharmacy sequence. The courses in pharmaceutical and medicinal chemistry and pharmacology have also been quite successful in correlating a wide variety of facts concerning drug properties and action. But some one colloquium embodying the content of the pharmaceutical, physical, chemical, and biological areas would seem to be indicated in the final year of the curriculum. Perhaps others have developed such a course and will help us to formulate a concrete proposal during this week.

I am delighted to have spoken to you again on physical pharmacy. I hope that without refuting all that I have said in the past, I have presented the topic

in a slightly different way and have introduced sufficient new ideas so as to stimulate further expressions of agreement and disagreement. Then, as a result of our discussions here, physical pharmacy can serve its role better in the pharmaceutical sciences.

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APPENDIX 1

Physical Chemical Principles in the Pharmacy Curriculum

I. Introduction
   A. Dimensions and units
   B. Theory of errors

II. Structure and Properties of Matter
   A. Atomic and molecular structure
   B. Energy and the states of matter
      1. Gases, liquids and solids
      2. Heat and work
   C. Physical properties of molecules

III Solutions
   A. Definitions, concentration expressions
   B. Ideal and real solutions
   C. Colligative properties
   D. Theories of solutions
   E. Ionic Equilibria in various solvents
   F. Buffers and isotonic buffered solutions
   G. Electrochemistry and oxidation-reduction in pharmaceutical and biological systems
   H. Solubility of nonelectrolytes, weak electrolytes and strong electrolytes
   I. Diffusion; distribution between solvents; and drug extraction
   J. Complexation and binding in pharmaceutical and biological systems. Discussion of both metal ion and molecular organic complexes

IV. Drug Stabilization and Biochemical Kinetics
   A. Elementary calculus in chemical kinetics
   B. Chemical kinetics of drug decomposition.
   C. Stabilization of pharmaceutical systems
   D. Accelerated testing methods

E. Kinetics of drug absorption, distribution, and elimination
F. Dosage forms showing prolonged-release characteristics
G. Enzyme kinetics

V. Disperse Systems
A. Preparation, properties and stabilization of colloids
B. Interfacial phenomena, surfactants and solubilization
C. Micromeritics and powder dosage forms
D. Rheology of pharmaceutical dispersions and biological systems

VI. Design and Formulation of Pharmaceutical Products
A. Solutions: aqueous, nonaqueous and mixed solvent types, preservatives, colors, flavors
B. Emulsions, suspensions and solubilized products
C. Gels and other semisolid preparations
D. Loose powders, compacted and compressed dosage forms

APPENDIX 2

Physical Chemical Principles in Pharmacology

I. Introduction. Diffusion, Rate and Equilibrium Processes
A. Physical chemical factors involved in the release of medication
B. Absorption of drugs from the gastrointestinal tract
C. Absorption of drugs through the skin
D. Penetration through capillary walls and cell membranes

II. Absorption Distribution and Elimination of Drugs
A. Solubility, acid-base properties and other factors in relation to absorption
B. Rate of distribution, and equilibrium tissue concentration
C. Binding of various drugs to proteins in the plasma
D. Tissue depots and drug solubility
E. Duration of action and biochemical inactivation (drug metabolism)
F. Rate of elimination

III. Mechanism of Action
A. Structure and biological activity
B. Stereoisomerism and drug action
C. Nonspecific vs. specific drug action
D. Binding of drugs to receptors
E. Enzyme kinetics and metabolite antagonism
F. Metal complexation and drug action

APPENDIX 3

Physical Chemical Principles in Pharmaceutical and Medicinal Chemistry

I. Atomic and Molecular Theories
A. Electronic structures of drugs
B. The chemical bond, sigma and pi bonds
C. Secondary valence forces
D. Stereochemical features of drug molecules
E. Coordination compounds and the ligand field theory

II. Polarization and Steric Effects
   A. Electronegativity
   B. Inductive effect
   C. Resonance effect
   D. Steric effect

III. Reaction Rates
   A. Review of chemical kinetics
   B. Absolute reaction rate theory and postulated structures of the activated complex
   C. Factors affecting rate of reaction
   D. Isotope effects

IV. Reaction Mechanisms
   A. SN 1 and SN 2 reaction types in inorganic and organic systems
   B. Polar and ionic reactions
   C. Radical reactions; one-electron versus two-electron transfers
   D. Molecular (four-center) reactions

V. Structure-Reactivity Relationships
   A. Inductive and Resonance Effects
   B. The Hammett $\sigma\ \rho$ equation and modifications
   C. Bronsted catalytic law
   D. Steric effects in reactivity

VI. Physical Chemical Properties of Medicinal Agents
   The relation of functional groups, electronic and steric properties as they relate to pharmaceutical characteristics of drug molecules
   A. Solubility
   B. Acid-base properties
   C. Oxidation reduction and other electrochemical properties
   D. Complexation properties
   E. Color, taste and odor as related to molecular structure
   F. Mechanism of reactions involved in specific drug synthesis
   G. Mechanism of specific degradation reactions
   H. Chemical properties as related to modes of pharmacological action

PHARMACEUTICAL TECHNOLOGY

EUGENE L. PARROTT

After years of planning, tentative curriculum revisions, seminars, and untold faculty discussions, the five year program has finally become a fact. Despite serious preparation, there still exists confusion in regard to definitions and contents of courses to be taught. One of the purposes of this seminar is to permit the exchange of ideas and experiences that we have undergone in preparing the new curriculum. By such an exchange, the technical courses in pharmacy can be fashioned and modified throughout the nation to include essentially the same knowledge, skills, attitudes, and objectives. It is not necessarily desirable to have a stereotyped series of courses of identical titles and contents, for such conformity might preclude an indispensable reevaluation and modernization of our program as our technology expands. It is more fitting to have a general syllabus covering all technical pharmacy courses and to have each college adapt the syllabus to best fit the particular circumstances under which it operates.

The general objectives of the technical pharmacy courses are fourfold:

1. To impart a comprehension of physical and chemical principles, which are pertinent to pharmaceutical problems, phenomena, and preparations, and which can be used to understand and to predict the behavior of new pharmaceutical systems.
2. To develop skills and techniques upon which pharmaceutical processes are dependent through actual use of instruments, equipment, and laboratory manipulations.
3. To teach professional and scientific terminology which will enable the pharmacist to express himself as an educated person as well as to read current literature.
4. To promote judgment based on logical, imaginative and critical thought.

Let us consider these aims in more specific terms of pharmaceutical technology. In some colleges Physical Pharmacy has been accepted, but it is often taught after the classical physical chemistry pattern ignoring or employing few pharmaceutical systems. Properly aware that skills and techniques are important, many schools retain the old, little changed Preparations course. While both of these courses contain valuable knowledge and skills, it is a disservice to the student to present them as separate entities. It has been said that an integration of the two is not easily accomplished (1). If this is true from the viewpoint of the educator, imagine what a tremendous task it is for the undergraduate student to combine and correlate these courses on his own initiative. It is our obligation as teachers to integrate and to present a better organized series of courses so that the student may more easily obtain a complete appreciation of pharmaceutical systems.

Under the five year program the area of pharmacy suffers from prerequisite difficulty. Physical Pharmacy is often a diluted course due to lack of adequate mathematical background. With some departments of mathematics revising their courses into an integrated analytical geometry-calculus concept, the future is bright in regard to the type of mathematical training available; however, the future is rather bleak when the subject of mathematical prerequisites is brought before our own college administrators! Lacking calculus and two semesters of physical chemistry taught by a department of chemistry, it appears that the most versatile pharmacist can be produced by providing our students with an intermediate level course of the integrated type (2, 3, 4).

The term physical pharmacy is one of historical importance. With its advent, physical pharmacy introduced a new concept of quantitative characterization to pharmacy (5). The concept has been taught to and accepted by the more recent graduates of our schools and by many teachers of pharmacy. The concept has arrived as an appreciated part of our area; therefore, let us recognize that it is no longer necessary to defend the concept by a separate title or course but to accept the physical and quantitative approach as an intimate and continual part of the entire sequence of courses in technical pharmacy.

In technical pharmacy courses, we are concerned with properties and means of classifying properties of drugs, adsorption, novel dosage forms, extraction, solubility, polyphasic systems, preservation, formulation, controlled drug release, patient acceptance, sterilization, packaging, stability, and rate processes. Thanks to the leadership of the Wisconsin clan, the last decade has seen remarkable progress in placing the presentation of these topics on a firmer physical and mathematical basis with a deemphasis on descriptive education. This concept should be accepted in all of our technical pharmacy courses, and when it is accepted, there emerges an area of pharmacy which integrates the skills and techniques of preparation and evaluation of pharmaceutical systems with theoretical and quantitative characterizations. This area is pharmaceutical technology.

Pharmaceutical technology should be given in the professional years after the completion of all basic science courses. Ideally, the basic courses would consist of general chemistry, analytical chemistry, physics, organic chemistry, calculus, physical chemistry, and biology (6). The few fortunate schools operating on a six year program appear to have these requirements and can be excluded from our discussion. For schools operating on the five year program it is hoped that a more uniform standard of basic science preparation will be established when the concept of preprofessional training with a two year prepharmacy curriculum has been accepted by pharmaceutical education (7). At present, most five year programs are forced to compromise these prerequisites somewhat; nevertheless, within the curriculum, the limited mathematical knowledge our students possess can be integrated with theory and application to largely eliminate the empirical approach while promoting the application of physico-chemical principles to pharmaceutical systems.

The course content of pharmaceutical technology can be conveniently divided according to physical state into solids, solutions, polyphasic systems, and plastic systems. A schedule of three lectures and one laboratory weekly for a minimum of two semesters and preferably for three semesters would permit the coverage outlined below.

Syllabus of Pharmaceutical Technology

Solids

I. Particle Size Measurement
   A. Optical Microscopy
      1. Terminology
         a. Frequency
         b. Size-frequency curve
         c. Limitations and definitions of means
            1) arithmetic mean diameter
            2) mean volume diameter
            3) mean volume-surface diameter
   B. Sieving
      1. Standard sieves
      2. Terminology
         a. Geometric mean diameter
         b. Standard deviation
         c. Probability paper
         d. Hatch-Choate Equation
      3. Application of statistical method
   C. Sedimentation
      1. Method
      2. Particle number
      3. Specific surface
   D. Others: adsorption, elutriation, permeability (as time and equipment permit)

II. Characteristics of Powders
   A. Packing
   B. Densities
      1. True
      2. Granule
      3. Bulk
   C. Flow (repose angle)
   D. Porosity

III. Reduction of Particle Size
   A. Methods
   B. Evaluation of dental and body powders, aerosols

IV. Properties of Solids
   A. Water in solids
      1. Deliquescence
      2. Efflorescence
      3. Constant vapor pressure mixtures
      4. States of water: water of crystallization, hygroscopicity, imbibition
   B. Liquefaction of mixture of solids

V. Relation of Particle Size to
   A. Time of vs. rate of solution (Noyes-Whitney)
   B. Solubility (Dundon-Mack)
   C. Chemical activity (dust explosions, combustion)
   D. Adsorption
   E. Therapy
      1. Oral (sulfa, Cathomycin)
      2. Parenteral (Lente insulins)
      3. Topical
   F. Efficiency and methods of blending
   G. Galenical Extraction

VI. Granulations and Powders
   A. Granule (spray drying)
   B. Effervescent granules
   C. Bulk and divided powders
   D. Encapsulated powders
   E. Microencapsulation

VII. Molded Dosages
   A. T. T.
   B. Pill
   C. Troche

VIII. Compressed Dosages
   A. Techniques of tableting
   B. Physics of tablet compression

IX. Coating
   A. Sugar
   B. Air suspension
   C. Spray
   D. Press
   E. Special: enteric, delayed action, etc.

X. Testing of Solids
   A. Hardness
   B. Disintegration or Solution
   C. Weight variation

Solutions

I. Viscosity

II. Interfacial Tension

III. Solubility
   A. Concentration expressions: molal, molar, etc.
   B. Ideal vs. nonideal
   C. Solvent-solute interactions
   D. Raoult's law
   E. Solubility product

IV. Aqueous Solutions
- A. Henry's law
- B. Dalton's law
- C. Distillation
- D. Pharmaceutical classification
  1. Water
  2. Syrup
  3. Solution
- E. Preservation

V. Nonaqueous Solutions
- A. Solvents employed
- B. Pharmaceutical classification
  1. Elixir
  2. Spirit
  3. Liniment
  4. Solution
- C. Extraction procedure
  1. Partition coefficient
  2. Techniques (A through E)
  3. Pharmaceutical classification
     a. Fluidextract
     b. Tincture
     c. Related: oleoresin, resin, extract

VI. Flavor
- A. Physiology of taste
- B. Technique
  1. Masking
  2. Carbonation
  3. Emulsification
  4. Insoluble colloidal form
- C. Relationship of odor to taste
- D. Pharmaceutical and cosmetic applications

VII. Color
- A. Theory
- B. Psychology
- C. F. D. C. Regulations
- D. Properties of dyes

VIII. Colligative Properties
- A. Lowering of vapor pressure, elevation of boiling point and osmotic pressure
- B. Lowering of freezing point
- C. Practical calculations for isotonic solutions

IX. Buffers
- A. Review: Mass action, pH, K_a, K_w, etc.
- B. Electrochemistry
  1. Specific resistance and conductance, equivalent conductance
  2. Conductivity measurements
  3. Electromotive force
- C. Buffer systems
  1. Henderson-Hasselbach Equation
  2. Buffer capacity
  3. Examples
- D. Relation of pH to
  1. Stability in solution
  2. Preservative action
  3. Drug absorption
  4. Extraction procedures
  5. Incompatibilities
  6. Total solubility

X. Parenteral Solutions
- A. Routes of administration
- B. Methods of sterilization
  1. Heat
  2. Gas
  3. Radiation
  4. Filtration
- C. Tests for sterility
- D. Pyrogens
- E. Vehicles
- F. Preservatives
- G. Containers

XI. Kinetics
- A. Hydrolysis
  1. First order
  2. pH effect
  3. Temperature effect
- B. Oxidation
- C. Photochemical
- D. Applications
  1. Accelerated stability studies
  2. Autoclaving

Polyphasic Systems

I. Colloids
- A. Characteristics
  1. Tyndall cone
  2. Brownian movement
  3. Electrical properties and zeta potential
- B. Emulsoid vs. suspensoid
- C. Protective colloid
- D. Preparation
- E. Solubilization

II. Suspensions
- A. Sedimentation
  1. Suspending agent
  2. Stokes' Law
- B. Newtonian vs. non-Newtonian
  1. Thixotropy
  2. Plastic
  3. Pseudo-plastic
- C. Pharmaceutical classification
  1. Lotion
  2. Magma
  3. Mixture
  4. Suspension
  5. Parenteral suspension

III. Emulsion
- A. Surface active agents
  1. Characteristics
  2. Classification
     a. Chemical
     b. Ionic
  3. H. L. B.
- B. Emulsification
  1. Types
  2. Technique
  3. Work involved and effect of surfactant
  4. Stability

Plastic Systems

I. Suppository
- A. Bases
- B. Polymorphism
- C. Release of drug

II. Ointment
- A. Bases
- B. Preparation
- C. Percutaneous absorption
- D. Interaction between drug and base
- E. Related: pastes, toothpastes, etc.

III. Gels

Since rate processes are discussed in other divisions of pharmaceutical science, the coverage of rate processes in pharmaceutical technology is limited to drug stability. Radiochemistry and decay curves are studied in pharmaceutical chemistry. Drug elimination and absorption, tissue half-life and kinetics, and detailed sustained release studies are presented in the final year course in pharmacy, because it is felt that concurrent study of pharmacology enables the student to understand these phenomena more thoroughly.

Atomic and molecular structures are presented in general and pharmaceutical chemistry. Dimensions and units are covered in physics and general chemistry. Thermodynamics is largely ignored because of poor mathematical background; however, as required, certain concepts may be used but no attempt is made to adequately cover the topic.

The topics will vary somewhat from school to school depending on the coverage of material in the basic science courses and in courses within the school of pharmacy. Here there is vital need for discussion and cooperation among the faculty as to how overlapping subjects can best be handled for each individual school.

A serious failing in pharmaceutical science is that students and graduates are not able to solve new problems. Not only must we teach these topics from the viewpoint of facts and techniques, but by providing practices in problem solving, we must force the student to see the relation of theory to final result. In other words, we should strive to get our students to think.

In general, the coverage of any topic should include theories pertinent to pharmaceutical systems so that, regardless of future changes, the pharmacist knows fundamental relationships which he can independently apply as new problems arise. Emphasis should be on the relationship of physical properties and functional groups of drugs to formulation, stability, and availability problems. Since textbooks in pharmaceutical technology are non-existent, it is vital to present material from research and technical papers as a supplement to whatever arbitrary text one selects for his course. To facilitate study, appropriate homework should be assigned periodically. This will also give the lecturer an opportunity to evaluate the success of his lectures which are the prime source of information for the student.

To illustrate the depth of coverage, let us consider colligative properties. The discussion of colligative properties may begin with Raoult's law for the lowering of vapor pressure. The Clausius-Clapeyron equation is a good starting point for the development of the elevation of the boiling point equation. Then by combining Raoult's law and Clausius-Clapeyron equation the freezing point depression is derived. Osmotic pressure is discussed from the physiological as well as from the physico-chemical viewpoint. Methods for the determination of each colligative property are compared to show why the freezing point depression method is used in pharmacy rather than direct measurement of osmotic pressure. It is shown how the sodium chloride equivalent may be derived from basic thermodynamic equations. Other selected methods of calculating isotonicity are presented.

The theoretical lecture material is followed by a laboratory exercise for the determination of the freezing point using the Beckmann molecular-weight apparatus (8). Actual formulation problems, which require independent measurements and adjustment to prepare an isotonic solution, are given to the student. Further appreciation of applied theory is gained when the student prepares hypertonic, hypotonic, and isotonic solutions which he instills in his eyes for comparison. Isotonic calculations permit direct use of lecture and text material in solving problems encountered at the level of the community pharmacist, as well the industrial pharmacist.

In discussing emulsions, the characteristics of surface active agents are made more realistic and meaningful by presenting the student with a dimensional pic-

ture of the surfactant. In the laboratory, the student determines the cross sectional area of a surface active agent (9). This is followed by a formulation problem in which the student is given a related surfactant and asked to calculate how much surfactant is necessary to emulsify a given volume of an oil to a particular average globular size. This exercise is repeated at several globular sizes to illustrate the principle that, all other factors being constant, the amount of emulsifying agent limits the size to which the globules of an emulsion may be reduced. This may be evaluated by optical microscopy.

In general the laboratory should be designed so that the answers can not be found in print but must be experimentally determined or arrived at by logical deduction. When possible the initial portion of the experiment should be of a theoretical nature followed by exercises which utilize the theory in an applied or practical manner. It will motivate the student to learn if he identified the material to be learned with a recognized need for it.

For convenience, a laboratory manual should be available so that the student may study and plan the exercise prior to actual experimentation or preparation. It is helpful to both the student and the instructor to have a brief discussion with each laboratory. New instruments and apparatus are demonstrated so the student acquires some incidental skills and techniques in elemental instrumentation. During the discussion the instructor can caution against pitfalls in the exercise, discuss the theory of errors involved, and make certain that proper skills and techniques are employed. It is in the laboratory where the proper correlation between theory presented in lecture and the exercise must manifest itself. Judgment must be developed in the laboratory as well as skills and techniques.

Notebooks are initialled by the instructor at the completion of the actual experiment, and they are taken home for evaluation of data and the formation of conclusions. Such a procedure makes certain that the work is actually done, yet it allows time for the student to reflect upon and assimilate the exercise.

In conclusion, it seems that in the best interest of the student the courses conventionally known as Preparations, Physical Pharmacy, and Pharmaceutical Technology be integrated into a related sequence of courses. Possessing continuity, this sequence may appropriately be called pharmaceutical technology. The important thing is that, regardless of nomenclature, pharmaceutical technology be presented in a physical and quantitative manner.

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FOURTH OR TERMINAL COURSE IN PHARMACY

JOHN AUTIAN

In the last several years practically all segments of pharmacy have come under the close surveillance of local, state, and Federal investigating committees. The Kefauver committee's reports, on the whole, were not very complimentary toward certain practices engaged in by our ethical pharmaceutical industry. The general publicity given to some of the testimony in these hearings was even more critical of industrial practice and, in many instances, stories were fabricated or distorted out of complete context to the actual facts presented. Even though the attack was directed toward industry, the back wash of emotions stirred up by the investigation was indirectly heaped upon the pharmaceutical practitioner who suddenly found himself in the uncompromising position of defending and justifying certain questionable practices either engaged in or at least purported to be engaged in by a number of companies making up the bulk of our pharmaceutical industry.

The Kefauver investigations thus set the stage for a second act in a real live melodrama where pharmacy became a leading player. In this instance, and to the sorrow of those interested in pharmacy, the pharmaceutical practitioner in retail practice emerged as the villain. Of course, I am speaking of the charges which have been brought against a number of pharmaceutical associations by the Justice Department. The prototype of these cases can be reviewed by looking at what occurred in California. Here, the retail pharmacist was pricing his prescriptions according to a pricing schedule suggested by a regional association. The Justice Department contended that what was being done was in direct violation of Federal legislation and was, in fact, "price-fixing." The legal council for the Northern California Pharmaceutical Association with direct financial support from the American Pharmaceutical Association rejected this charge and maintained that pharmacy practice is a profession, and the filling of a prescription is an act of professional service not to be interpreted as just the selling of a product.

It soon became clear that this decision would have one of the most dramatic effects on professional pharmacy in this country. A decision in favor of the Northern California Pharmaceutical Association would give solid, legal support that pharmacy is a profession, while a decision rendered in favor of the Justice Department would place pharmacy practice—as now practiced—on the level of retail merchandising. After many heated arguments on both sides the verdict was made against pharmacy and a fine of $40,000 placed against the association.

The results of this decision against pharmacy and perhaps of other decisions to come will undoubtedly have far reaching consequences on the profession of pharmacy. Even though the outcome of this particular trial is an extremely bitter pill to take, we perhaps should not have been too surprised at the court's decision. A cursory analysis of past and present retail pharmacy operation would have

spelled out in the minds of objective, intelligent people that many functions of the average drug store could in no way be interpreted as a unique, professional service to be rendered in the spirit of improving the public health of the community. The fact that there was a need for expensive legal council by a professional organization to defend its professional character, in itself, is an indictment that "all is not so well in pharmacy." A hasty recourse by good-intentioned people to proclaim with loud voices and words that the pharmacist is a member of a public health team who uses his educational background to make decisions in the interest of public health when he is filling a prescription is a portrait skillfully painted but by no means depicting the picture as seen daily by the millions of customers entering the various drug stores throughout our great country.

I am not condemning the action taken by the American Pharmaceutical Association or other interested parties to defend in court the life of pharmacy as a profession, but rather questioning the present structure of retail pharmacy practice which has led to a need for an investigation by the Federal government, who, after all, represent the wishes of the majority of our people. Clearly, it appears that pharmacy cannot rely on the retail practitioner to lead in elevating our profession. The leadership must come from our own ranks, the pharmaceutical educators.

We have reached a critical if not a very historical point in our profession of pharmacy. The question which faces us today is to define clearly what we expect of pharmacy in the future. If we wish for pharmacy to take on the role of a real member of the public health team, then we must, through our schools, indoctrinate and educate our students to fulfill this role. Specifically, I feel that our terminal pharmacy course can help to prepare our future pharmacist for the professional role we all would like to see—providing that this present course be drastically revised.

When I accepted this invitation to speak before this learned body, which represents the best minds in pharmacy education, on the subject of the fourth or terminal pharmacy course, I felt that I could cover the subject in a relatively short discussion. I have since realized that this was an extremely naive thought on my part and now I can only inform you that my presentation will follow the pattern of an oil painting which has been hastily sketched with the least number of brush strokes—enough to convey an image, but not necessarily an exact or well defined image.

My purpose, or more rightly my objective, in presenting this talk, is to convey to you my deep conviction that our present fourth or terminal pharmacy course should be completely revised in order to prepare our future pharmacist for a role more professional in nature and one which will become accepted by our medical brothers and sisters as a necessary and useful function. This role of the pharmacist of the future should be directed toward one advising the medical practitioner or other para-medical personnel on the selection of drug products. For convenience then, I have chosen to divide this talk into two general parts. The first part will be devoted to the need for a change in the terminal pharmacy course, while the second will deal with the course content itself.

PART I

NEED FOR CHANGE IN THE TERMINAL PHARMACY COURSE CHANGING PATTERNS OF LIFE IN THE UNITED STATES

We are part of a larger group, and changes which have and do take place in society will also influence our own behavior. In fact, it would not be a misstatement to say that socio-politico-economic forces will undoubtedly bend, sway, and even break our professional character if the proper situation presents itself. We are living in a population boom which will become a population explosion. We are living in an era of advanced technological and scientific achievements where labor and automation compete with each other. We are exploring space and spending huge sums to defend our nation. We are fast reaching a status where most Americans are receiving substantial education up and into college. We are becoming suburban communities which in turn are reaching out into the countryside and finally linking up to other suburban communities. We are becoming better fed, better hospitalized, and better cared for in every way. We are indeed a part of society, and all these movements and forces are the seas which pharmacy sails on. These forces are also responsible for the dual role pharmacists play in the practice of retail pharmacy, on one hand a business man while on the other a professional man. Even the professional role has been challenged and this in part might be traced to the influence of the pharmaceutical industry which has been able to create and produce outstanding medications in such convenient dosage forms under trademarked names. So expertly are these complex medications formed into convenient dosage forms that all the pharmacist has to do is to read the prescription and then transfer that particular medication from the company's container to a prescription container.

As the professional image of retail pharmacy has dwindled, quite another trend has taken place in hospital pharmacy practice. Today in many hospitals, the hospital pharmacist has emerged as a very important and integral part of the hospital staff. The development of the formulary system and active participation of the chief pharmacist on various committees in the hospital has given the hospital pharmacist the opportunity to act as a true consultant. The importance of hospital pharmacy may be appreciated if one considers that approximately 30 per cent of all ethical drug products are distributed through hospital pharmacies.

Pharmacist of the Future

The role of the future pharmacist will most likely follow the road leading to that of an advisor or a consultant. It will be necessary, of course, in the future to have the actual role of the pharmacist in professional practice clearly defined. At present this role takes on the portrait of a business man mixed into a professional man. We cannot afford to have this dual role continue for too long or else the value of one will suffer. It is hoped that in the future the business practice as seen in many drug stores will give way to those practices where services are rendered which will promote public health. We cannot nor should we ever forget that our first duty is to the health of our community. This leads to the meaning

of consultant which, as we are all aware, means many things to many people. For my part I would like to define the term as follows:

> A pharmaceutical consultant is a pharmacist who advises and performs services to those seeking knowledge or products which can be considered as special for which he (the pharmacist) has accumulated theory and knowledge by education and experience. Furthermore, the pharmacist—if the need is justified—will make available one or more of his facilities to implement his counseling or consulting. (1)

I am hoping that the future will bring a form of independence from the influence of the pharmaceutical industry and other pressure groups. At the same time, however, there should be greater cooperative interplay of services between and among the various specialty groups forming the complex team referred to as the public health team. Undoubtedly, this independence will be achieved if the future pharmacist is elevated to the position of a true adviser to the physician on matters pertaining to drug products.

In most instances, the pharmacist of the future will play less of a role as a technician and, in fact, it may come about that the pharmacist will employ a technician to handle the routine manipulations which might be necessary in dispensing a drug product, while the more judgment type of activities will be entrusted solely with the pharmacist.

It will be inevitable, if the future pharmacist becomes a consultant, to have a more understanding system of communication with the physician. The language of the physician must not only be understood by the pharmacist but a greater appreciation and knowledge of clinical medicine will be necessary for the pharmacist to discharge his future duties.

In the field of hospital pharmacy and in those clinical and community pharmacy practices, the pharmacist should have an even greater role as the advisor. The hospital pharmacist has already demonstrated his contribution to this endeavor by helping to initiate formulary systems and by contributing his knowledge and experience to numerous groups throughout the hospital; his number will increase in the future. Greater use will also be made of the community pharmacist in rural areas by small hospitals in those areas.

Most likely the future pharmacist will have six years of education and will graduate with a Doctor of Pharmacy Degree. These young men and women will not be content to endure a number of practices presently seen in the modern drug store but will, instead, want to establish themselves on a professional level consistent with professionalism. The social implications of a Doctor's degree will understandably have its impact upon the general public as well as other members of the health profession. In short, the future pharmacist will become a specialist on the matter of drugs and will be able to suggest to those interested the best possible medication for a specific malady. Other ancillary functions will be necessary but these again will reflect the educational background needed for the future pharmacist. The day of the beach ball and the fountain may be a happy thing of the past in the professional drug store of the future.

Development of Courses in "Compounding and Dispensing" in the United States

I would now like to come back to the subject at hand—the fourth or terminal course in pharmacy, commonly referred to as the "compounding and dispensing" course. Historically, this course has paralleled the actual practices of retail pharmacy of that period. In the nineteenth and early twentieth centuries,

this course was one of manipulative skills, and the knowledge needed for the course was primarily that of facts. Since science was still to come to pharmacy, galenical pharmacy and its various ramifications were basic constituents of the compounding course. The great pharmacists of the past such as Protor, Parrish, Squibb, Remington, etc. each added his own particular contribution to pharmacy which, in turn, was then incorporated into the course.

As the pharmaceutical industry took over the compounding role and, in turn, created prepackaged dosage forms of new synthetic agents, the classical compounding by the retail pharmacist declined. Since these new medications and their various dosage forms were starting to multiply in gigantic proportions, it appeared to be necessary to include in the dispensing course the trademarked names of all these products as well as their general uses. For the most part, however, little concern was given to the actual benefits of these dosage forms or whether one product may or may not be better than existing drug products. In some dispensing courses, the actual appearance and the various strengths of the dosage form with the unit cost became an important part of the student's classroom sessions. The laboratory periods were devoted to countless preparations of prescriptions and incompatibility experiments based upon empirical considerations.

While other courses in pharmacy were starting to feel the need of revision and rejuvenation, this same philosophy was not evident to those in charge of the dispensing course. Part of this lack of desire to change to a more scientific approach or a more medical oriented approach probably stems from the continual pressure of the state boards of pharmacy and retail pharmacy in general to emphasize the very practical aspects of retail pharmacy. Part of the responsibility must also be shared by those of us who have taught this course. We have not wished to tamper with a "sleeping dog" for fear that the active dog might make it necessary for us to make some changes.

A Time for Change in Course Content of Terminal Pharmacy Course

Advancement in science and technology and their direct and indirect influence on medical practice have created a host of new therapeutic, diagnostic, and nutritional agents with dosage forms so far advanced from the "old days" that the actual pharmaceutics or the product may determine the effectiveness of the active ingredient. No longer can the physician or other para-medical person cope with all these drugs, their actions, side effects, and perhaps even their effectiveness. Should not the pharmacist now step into this picture and become the expert on drug products?

The pharmacist should take on a new role in the future and his training must prepare him to meet the requirements of an expert on drugs and drug products. This role should become the main professional service he, the pharmacist, can render. Brodie and Meyers have already suggested that the hospital pharmacist should act as a drug consultant but they are quick to point out the following:

> Quite often when the pharmacist is cast in the role of consultant he would be more accurately portrayed as an informant. A pharmacist can provide a physician with the name, source, dose, use, price, therapeutic equivalents and physical properties of a drug, serving well as an informant, but actually falling considerably short of performing the service that a consultant might provide under the same circum-

> stances. The drug consultant, in addition to the above information, should be able to provide a discriminatory evaluation of the drug in question and supply a professional judgment, if requested, regarding rational therapeutic use of the agent or equivalent agents. (2)

I would like to extend this role not only to the hospital pharmacist but to those other pharmacists in retail or clinic pharmacies. It appears to me that the time is ripe for us, the pharmaceutical educators of this country, to step forward and take the challenge of creating the new pharmacist of the future. After all, should not the leadership come from our group, vested by education, tradition and given academic privileges by society to create new ideas which in turn might improve existing situations? If new ideas are not to flow from the corridors of our schools of pharmacy, or if these ideas are to be stifled by vested interest, can we expect the future pharmacy practitioner to portray himself in a light which will ensure professional respect from other members of the public health team?

The fourth or terminal course in pharmacy would seem to be the logical place for presenting subject matter which will equip the student to become a drug consultant. Even though our pharmaceutical literature in recent years has played up the drug consultant role in various ways, little information or suggestions have been included as to what the schools of pharmacy might do to implement the student's background for this role of consulting. Dr. Alex Berman and I, several years ago, felt that the present dispensing courses should be completely revised and that a new concept should be ushered into the course dealing with drug evaluation. It was reasoned that if the pharmacist could make critical judgments concerning one drug product in comparison with other drug products, then a unique and special service would become available to the medical practitioner. Our ideas were finally embodied in a paper entitled, "Concepts of Drug Evaluation in the Dispensing Course of the Future" which appeared, as many of you know, in a recent issue of the *Am. J. Pharm. Ed.* (3). Presently I should like to review what we and, perhaps, what some of you believe should be included in a dispensing course which will fulfill our desires for the pharmacist.

Need for New Name for "Compounding and Dispensing" Course

"A rose by any other name," or so it goes, "smells just as sweet." This, undoubtedly, is quite true, but to many the aroma from the term "compounding or dispensing" does not fill the nostrils with fragrance of enchanted lands. There is a definite need to replace this title in the future with a more suitable name. I believe that a new name such as *Clinical Pharmacy* may bring much responsibility and perhaps even a little glamour to this terminal pharmacy course. I will, however, for the present refer to this new course only as the *Terminal Pharmacy Course* and permit those much wiser than I to coin a more useful name.

PART II

CONTENT OF FUTURE COURSE IN FOURTH YEAR OF PHARMACY OR TERMINAL PHARMACY COURSE GENERAL REMARKS

What is to follow should be considered as suggested topics which might be included in the new revised terminal course. It will become apparent as we proceed that each school will have to decide on the merits of the topics as well as the need to include them in the terminal course since, depending upon a par-

ticular school, one or more of these topics may have already been included in previous courses. Furthermore, I would like to emphasize that this course should serve as a focal point where past facts and theories can be woven into a well-organized pattern which can give to the student a methodology to serve as a drug expert and consultant.

Topics to Be Included in Course—Lecture

1. **Communications.** If the pharmacist is to be successful, he must know the language used in medical practice. Too often today our students have little in the way of medical terminology. If a previous course has not included medical terminology, it must be introduced into this course as early as possible since it will be basic to nearly all which will follow.*

Even though to this group there is no question concerning the value of the library and other sources of information, our students seem to have little ability in searching the literature. This presents a difficult task to the teacher since time to follow the student to see if he is accomplishing his mission in using the library usually is limited. Guide lines, however, can be set up which will permit the student to approach literature from a more organized point of view. Later on in the course when drug evaluation reports are required, actual practice in literature survey can take place.

Good interprofessional relations demand good communication. The spoken as well as the written word must convey an exact meaning. Obviously, this is not a matter which can be taught in the Terminal Pharmacy Course. The merits and its implications, however, should be brought to the attention of the student. Again, the student will have the opportunity to present reports, both oral and written, and this should further serve to reinforce the extremely important emphasis on "communication."

It has been predicted that more students will enter hospital pharmacy practice in the future, and thus this course should familiarize the student with the pharmacy and therapeutic committees. As before, the mechanics of communication will be either one of helping the pharmacist or hindering his performance. There is no doubt that many community pharmacists will be aiding small hospitals. Proper communications will have to be maintained if both the hospital and the pharmacist are to advance the care of the patient.

A review of report writing may be included in this section of the course and its value demonstrated by actual reference to various reports which individuals or committees prepare. The student, depending upon the particular school, may not have had recourse to proper report writing for a number of years, and if it is not emphasized again there may be the possibility of the student paying little heed to this very important art of communication.

2. **Methods of Compounding and Dispensing.** There appears to be general agreement by a number of pharmacy teachers that the techniques of compounding and dispensing can be minimized in the terminal course. This feeling is, of course, based upon the premise that students entering the terminal course have been exposed in previous pharmacy courses to proper and well supervised instructions in the compounding and dispensing functions. No one should doubt the importance of the dispensing function for pharmacists since this is, at present,

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* Guess and Autian have suggested the use of Teaching Machines for certain subject matters in pharmacy (See: "Pharmacy and the Teaching Machine" to be published in the *Am. J. Pharm. Ed.*). Medical terminology would be an ideal course to use in a teaching machine.

the most important professional service which can be rendered. The point I wish to make, however, is that less time need be spent on routine phases of the art of compounding and dispensing. A few good lectures on this topic should suffice.

One of the lectures should include a discussion of the theory of errors and the actual limitations to accuracy which might occur when various dosage forms are prepared. The student must realize that his prescription cannot be 100 per cent accurate since his tools and techniques are not that sensitive. This should not be interpreted in any way as signifying that accuracy is to be minimized, but rather that a realistic approach to compounding problems in weights and measures is in order. After all, our students should have grown out of the older empirical approach to pharmacy in their previous courses.

A lecture or two on the receiving, processing, filling, dispensing, and recording of a prescription will be in order and actual practice of these acts can be included in the laboratory sessions. Some schools already have predispensing courses and if this is the case much of what has been included here may not be necessary.

3. **Theoretical Foundation.** Since the future pharmacist is to become a drug consultant, he must be familiar with the theoretical foundations of drug activity. Furthermore, the student should understand the effect the actual dosage may have on drug activity. Most of these points will have been presented in various courses throughout the student's college life, but the time has now come where these various viewpoints should be reviewed and brought sharply into focus. There is a great failing in present pharmacy education which permits the student to "forget" what he has learned in a previous course. The student will need help in organizing his thoughts on drug activity and the terminal course may act as a form of clearing house where the teacher may draw upon the student's past and sort of wrap-up the various theories into one composite structure with the usual limitations of each of the theories. Here homework or assignments may be given to the student to review various concepts used to explain drug activity.

A review of product formulation and stability may be introduced at this time, keeping in mind that the student has had an intensive course in physical pharmacy.

There will be a definite need for statistics in the future for pharmacy students if they are expected to understand control procedures as well as clinical evaluations. If there is no course in statistics then a very elementary course may have to be injected in this phase of the course. It is hoped, however, that in the future the present *Pharmacy Mathematics' Course* could be rearranged to include statistics. Some schools, no doubt, will have statistics and only the actual uses of statistics in pharmacy and medicine will be necessary. Actual practice may then be given in the use of statistics for clinical evaluations of new drugs. Finally, the limitations of statistics may be discussed.

I believe that the Terminal Pharmacy Course may have to introduce the science of experimental design and how physico-chemical experiments and biological experiments are organized in order to give meaningful, yet true results. It is gratifying to learn that even now some schools are introducing this very important subject.

4. **History of Drug Evaluation.** Perhaps it is not too surprising that little has been written in respect to the history of drug evaluation. It has been only in

relatively recent times that even medicine has approached the subject of drug evaluation from a scientific point. For the most part drug evaluation has been based upon an empirical basis where improper or misinterpreted results were more often the case than not.

The pharmacy teacher will require help in developing this particular subject, but I am sure a suitable presentation will be possible by alluding to medical articles on drug evaluation. Even less information will be available on pharmaceutical evaluation, at least with modern products, since often this type of information is kept behind closed doors in the various pharmaceutical houses. The various testing procedures are well known to all pharmacy teachers and these can be touched upon. Perhaps we can induce one of our historical scholars such as Dr. Alex Berman or Dr. Glenn Sonnedecker to develop this topic so that the rest of us may allude freely to it.

Under the history heading it will be very important to have the student recognize clinical centers such as the major university hospitals and the National Institutes of Health and their functions in the testing of new drugs. Laws governing new drugs and the moral implications of testing drugs on humans may also be included here.

5. **Development of New Drug Products.** The student must be made to appreciate the intricate steps required to produce a new drug product. Often the student is made to accept the fact that a new drug product is conceived and produced with little effort. Without really knowing the various steps and problems a new product must flow through, the student cannot be expected to intelligently discuss drug products. The points to be covered under this particular topic can be summarized as follows:

1. Concept of "Idea" for new product
2. Methods of creating new drugs
   a. Duplicate existing compounds
   b. Alter the structure of a known compound to produce a better therapeutic agent
   c. Synthesize a completely new compound for a specific purpose
   d. Develop an "exotic" dosage form
   e. Others
3. Animal experimentations needed for new drugs
4. Clinical trials
5. New drug application
6. Drug promotion

As you can see, each of these points can lead to very interesting lectures and the resourcefulness of the instructor in presenting this topic will for the most part determine the effectiveness and scope of the subject. The importance of the Pharmaceutical Industry in developing these new products and the inability of the practicing pharmacist to create the same products can be emphasized.

6. **Clinical Evaluation of New Drugs.** A point will be reached in the lecture series whereby a more thorough presentation of experimental design as used by clinical pharmacologists will be necessary. Here once again, the change from past empiricism to a more scientific approach is of recent times. This is partly due to a lack of qualified clinical pharmacologists and desires of certain groups to "rush through" a new drug for marketing. It is not implied here that the phar-

macist will ever do clinical evaluation, but if he is to interpret evaluation reports he most certainly must have a very good background in the methods currently used by clinicians to evaluate the effects of a drug. The points which should be discussed under human experimental design may be outlined according to the following pattern:

1. Subjective vs. objective method of evaluation
2. Selection of patients
3. Grouping of patients
4. Types of drugs to be used in experiments
   a. New agents
   b. Well-known agent
   c. Placebo
   d. Control
5. System of drug administration
   a. Double blind method
   b. Others
6. Collection of data
7. Evaluation of data
   a. Importance of statistics and its limitations
   b. Influence of "bias" results
   c. Use of figures and charts
   d. Conclusions
8. Types of personnel involved in clinical evaluation

Unfortunately time does not permit a complete discussion of the above point but information of this sort is now appearing in literature (4–6) and in texts (7–10).

7. **Drug Evaluation of Drug Products from a Pharmaceutical Point of View.** This topic should present less of a problem to the instructor since much of what can be reviewed here has already been given in one or more of the prerequisite courses. I will just mention points which may lead to some worth while discussions. These may be:

1. Esthetic qualities of products
2. Stability of product
3. Convenience of dosage
4. Value of extended forms
5. New dosage form
6. Others

Some information is starting to appear in journals concerning the pharmaceutics of drug products but for the most part little to none is available on new trademarked products.

8. **Dissemination of Drug Information.** Little emphasized in most pharmacy courses today is the importance that should be attached to the dissemination of drug information. For is it not due to this fact that drugs are finally written by the physician and dispensed by the pharmacist? This drug information (at times

quite biased) will reach the medical practitioner and pharmacist in a number of ways. The more important routes are as follows:

1. Learned journals
2. Text and other references
3. Information from medical representative
4. Information from company literature
5. Information from News Letters and from professional groups
6. Other sources

Here it might be appropriate for me to comment that the student should be well indoctrinated as to the various biases which might creep into the information which is directly disseminated from the company. Also it will be recognized that little information on a company product will be available concerning the pharmaceutical qualities of the product. The future pharmacist should have this information if he is expected to select one product as being more efficacious than four or five other products bearing the same generically-equivalent active ingredients.

9. **Evaluation of Drug Products by the Pharmacist.** Up to this point the student in this terminal course has been exposed to the various facets entailed in the creation, animal testing, product development and testing, clinical evaluation, and final distribution of drug products with product information to the medical and pharmaceutical practitioner. All of these topics as well as other alluded to in this particular discussion must be woven into a fabric which conveys to the pharmacist (student) a methodology which will help in advising a physician as to which drug product might be the best. It is this professional task which places the pharmacist on the exalted level of a true drug consultant, and, as may be deduced, this judgment will come through various sources of drug product literature.

The pharmacist must be able to collect various sources of information concerning a said drug product and then to organize the information in such a way that ready reference will be possible. It is indeed unfortunate that the medical and pharmaceutical practitioners are faced with such a host of new drug products, many of which are not really much better than existing products. However, in all instances, the claims of the manufacturer in one way or another imply that the new product in question has proven to be superior over existing ones. These claims must be looked into with an honesty and sincerity which will ensure a critical appraisal of the product. For this, the pharmacist must be willing to examine the active ingredient by referring to standard pharmacology texts. The active ingredient may actually be a derivative of an existing pharmacologically active and well established ingredient. Much general information can be gained by a review of the pharmacology of the agent or parent agent. Reference to papers on the new active ingredient (if it is really new) is thus in order. Here the instructor has the responsibility to review the experimental design for one or more new products to point out to the student the value of the information. I need not remind you that many of our present drugs can only be evaluated clinically by a subjective method, and for these studies it would seem to be mandatory that proper controls and a placebo be included. If the article does

not have these controls or a placebo as well as a number of other disciplines, then the student should be made to recognize the limitations of the conclusions reached by the authors on the "new drug" product. A recent article in the *Journal of the American Medical Association* points to the "therapeutic" effects that placebos can produce (11). In this study a new tranquilizer and energizer were employed in a psychiatric hospital and the results indicated that 53 to 80 per cent of the patients benefited from the new drugs. Only later did the clinicians discover that these two "new" drugs were, in reality, placebos. The authors of the above article have found that only ten per cent of published reports on drugs used in psychiatric practice meet minimum standards of scientific acceptability. Thus, the use of studies which have not included placebos would not merit great support. Many other instances could be cited in medical literature where studies on new drugs failed to meet minimum standards, and it will be the duty of the pharmacist to be able to ferret out these cases when evaluating a new drug product.

In all of his search, the student (and of course the pharmacist) must seek unbiased drug information. The American Medical Association has recognized the need for drug evaluation reports and is spending more time and space in its journal to bring these reports to its readers. In this matter it is interesting to note the July 8, 1961 issue of the *Journal of the American Medical Association* which is designated as the *Therapeutic Number* (No. 1). It contains a number of articles on drug evaluations and a review of drugs evaluated by the Council on Drugs during 1960. The American Medical Association plans to include complete monograms of these drugs and others in its annual publication, *New and Nonofficial Drugs*. Several recent journals *(Clinical Pharmacology and Therapeutics* and *Journal of New Drugs)* are attempting to meet the needs of the interested physician in accurate portrayals of drug activity. Various types of newsletters are also appearing which have as their objective a more rational evaluation of new drugs as well as some old ones. An example of this type of letter is *The Medical Letter* published in notebook fashion which can be inserted into a looseleaf binder. Texts on new drugs are also appearing, again attempting to present the actions of a drug in an unbiased manner. The above references as well as many others can serve the instructor in numerous ways to present this phase of the course to the student. The instructor should place a great deal of emphasis on these references since they will be or should be of great assistance to the student after he enters the practice of pharmacy.

The student, like many pharmacists and physicians, will be in a quandary concerning trademarked products versus generic named products. It is imperative that the student be informed that all generically named products are not inferior. Each must be considered with a view of objectivity rather than one of emotion.

The instructor must convey to the student that rational evaluation of drug products (actually drug literature or information) from the pharmacists' viewpoint must be based upon both the *therapeutic* and *pharmaceutical* considerations. If a number of drug products which are accepted as generically equivalent appear to have equal therapeutic potential with approximately the same side effects, then it becomes the duty of the pharmacist to make a critical judgment concerning the pharmaceutics of the product. This will include the stability, rate of drug release, particular dosage form, convenience of dosage form, esthetic

aspects of the product, packaging, and lastly the cost. Here it will be necessary to inform the student that all "exotic" dosage forms may not really be much better than conventional dosage forms when the price is considered.

Much information is now available for the pharmacist to make a decision on the merits of a particular drug from the point of view of therapeutics. Less data is at hand for the evaluation of the pharmaceutics of a new dosage form since this type of information is not readily available to the practitioner. It is hoped, however, that in the immediate future pharmaceutical concerns will make these reports available.

Now the question may be asked: How will the instructor be able to teach or lecture on methods of drug evaluation? At once it should be clearly understood that there is no intent here of indicating that the future pharmacist will be a clinical pharmacologist. The pharmacist, as it has already been explained, will devote his attention to the appraisal of drug literature in order to make suggestions about the worth of a particular drug. Since most drugs are now produced under trademarked names, it will be necessary for the student to have a method of evaluating the drug advertising for that particular product. Some attempts have been made in medical schools to do just this. Dr. Solomon Garb and the pharmacology department at the Albany Medical College, Albany, N. Y. have initiated a program on this vital subject. They have published two articles which should be of interest to those teaching in this terminal pharmacy course (12, 13). A great deal of exploratory work must still be done in this area and it is hoped that one or more enterprising pharmacy teachers will develop course outlines on the method or methods which can be taught to pharmacy students in order for them to act in the role of an evaluator. I need not emphasize that this topic must require careful handling and should become the most important subject matter in the Terminal Pharmacy Course.

10. **Non-Prescription Drug Products.** Several lectures should be devoted to over-the-counter medications which are continually appearing on the market and how, in general, these medications are more placebo type of drugs than real medications. Of course this is not always true, but the student should be made to realize that much of the demand created for these products is due to the unusually vast sums of money spent on promotion through radio, television and various lay journals and papers. The student should be made aware of his responsibility as a future pharmacist to be able to sift out the "fraud" in the advertising and to make it clear to his customers the real value of the product in relationship to existing products. The student's background in pharmacology should serve him well to detect the true worth (from a therapeutic effect) of these numerous, glittering products, which are, in many instances, nostrums. The emphasis here should be placed on the real value of the product and not on the thought of selling for the sake of selling.

11. **Professional Services Which Can Be Rendered by the Pharmacist.** Professional prestige and stature will climb directly in proportion to the good opinions of all those in one way or another connected with public health functions. The student should be taught the responsibility he has in this very complex organization, which in many respects is quite disjointed, and how he might better service their needs. Much has already been written on the subject of pro-

fessional services which can be rendered to the public health team and to the community, and thus I will be content just to mention those persons or groups which the pharmacist can serve:

1. The physician
2. The dentist
3. The nurse
4. Small hospitals
5. Patients and customers
6. Community

The time to be devoted to this topic in lecture will again be dependent upon the particular school and the sequence of course work already given to the senior student. It might be profitable in these discussions to direct the student's attention to the possibility of setting up in his future drug store a clinical testing laboratory where routine analysis of blood, urine, sputum, etc. can be performed for one or more physicians. In some areas of the country there is a great need for such service.

12. **Application of Drugs to Diseases.** I am afraid the consulting role will fail if we do not review current therapeutic agents. There appears to be a great resistance to the teaching of therapeutics in pharmacy schools, but I fully believe that we should take a reverse step in this matter and start including therapeutics. It would not seem unreasonable to include one whole semester on this topic. The instructor should first discuss the ailment or disease, including the etiology, symptoms, and signs and, finally, the recommended drugs with the prevailing thoughts on their efficacy. In reviewing the drugs, the instructor can include representative drug products which are claimed to be effective in combating ailments and then to point out their rightful place in the treatment of the disease. Here advantages and disadvantages of the pharmaceutical aspects of the product or products can be discussed in order to prepare the student for his future role. This final topic can serve quite advantageously for both the teacher and the student for it will now be possible to integrate past information and theory into the structure of rational drug therapy.

Functions to Be Included in Laboratory

The laboratory sessions may have general functions. These are:

1. Filling and compounding of all types of prescriptions
2. Learning to develop formulas for a particular dosage form
3. Testing various dosage forms

Only limited time should be spent on the filling of routine prescriptions. It is hoped that previous laboratory sessions have already prepared the student for the usual compounding techniques.

Special problems should be assigned to the student to formulate a specific dosage form. The student must plan the problem and follow the formulation to its end. Only the active ingredient and the method of administration desired should be given to the student. He must do the rest. Since the purpose of these problems is to instill in the student confidence and a proper "know-how," the instructor should serve only as a guide. After completion of the product, the

student will write a report on his problem, listing the literature he surveyed and other pertinent information which will support the value of the product.

During one or more of the laboratory sessions, the student should be given a dosage form to be tested for its pharmaceutical efficacy. Such testing as disintegration rates, color stability, and quality of coatings for tablets may be cited as examples for this testing program. These testing procedures should serve to create interest and appreciation as to the value of one drug product over another in regards to the pharmaceutical aspects of the product.

It will be apparent from the above remarks that more staff will be needed in the laboratory than most schools use presently for the dispensing course. Whether this increase in staff can be justified will depend upon the philosophy of the particular school and its available funds.

Conferences and Visits

A planned conference session once a week should be held with a small group of students to discuss certain problems in detail. This time may be spent to review medical and pharmaceutical literature, pointing out the value of the article and the information which is contained therein. It seems quite likely that in time, case methods of studies can be used on particular drug products. From time to time, assignments should be made to groups of students to present a complete evaluation on a new or old drug product. This should be a written report as well as one which can be delivered orally to the group. These drug evaluation sessions should include guests such as clinical pharmacologists, physicians, medical representatives, and other interested faculty members.

If the school is located near a clinical center, it may be possible to have the students attend conferences at the center on various phases of medical practice.

Credits

I would recommend that ten-credit hours for one semester or five-credit hours for two semesters be considered as optimal instruction for the Terminal Pharmacy Course.

Types of Teachers Needed for Future Course

From what I have related and the brief review of the course contents for this new terminal pharmacy course, it should be very clear that at the present time very few teachers in our colleges of pharmacy could teach all the phases of the subject. There is the hope, however, that in the future the younger faculty members interested in this type of course will be afforded the opportunity to study at a medical center in the area of pharmacology and therapeutics. I say younger members because this course must evolve and will require much time and effort, which in many instances is not possible by a well-established, senior faculty member since he is burdened with a great deal of administrative work. Actually, this course should contain a number of faculty members or guest lecturers who, in a sense, might be called experts on one or more particular topics.

I would also suggest that funds be sought from various sources to implement the suggested program by permitting the faculty member to do extensive studies in developing the program. Here is a wonderful opportunity for those interested to create rather than mimic.

Summary

The problem the pharmacist is facing today in regard to his professional status must be recognized by us, the pharmaceutical educators. If we are to have future pharmacists who, in a true sense, will be considered as drug consultants then we must decide now what steps we can take to hasten us to our objective. One big step toward our goal is to revise our present terminal pharmacy course to the program envisioned in this paper. Admittedly, the presentation on the course content was of a probing and suggesting nature, since no real course as outlined is presently given. Phases of what has been related on a very superficial level were given by this speaker while at the University of Michigan, and presently, at the University of Texas, Dr. Wallace Guess is experimenting with one or two of the topics described.

My fervent hope remains that greater support will be given by our group to the future role of the pharmacist in our undergraduate program. We must not sit by complacently believing that others will take the leadership. If my talk has stimulated and focused your attention on the need for a new terminal course in pharmacy, then my efforts have been well rewarded.

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CURRENT CONCEPTS IN SELECTED SUBJECT AREAS

GENERAL KINETICS AND DRUG STABILITY

DAVID E. GUTTMAN

An impressive number of publications dealing with the application of kinetic treatments to the problems of drug stability has appeared in the pharmaceutical literature within the past ten years. Research in this area, as evidenced by the number of published contributions, has shown an almost exponential growth. For example, twenty-nine such publications appeared in the *Journal of the American Pharmaceutical Association* in the five year period, 1955 to 1960, as compared with thirteen in the preceding five year period. A survey of this literature leads to the important observation that fundamental kinetic laws and relationships which characterize the velocities of chemical reactions are operant in many pharmaceutical systems. A consequence of this that is of more immediate and practical significance is that the mathematical and analytical techniques, the terminology, and the emphasis on controlled experiments, which are conventionally used by the chemical kineticist, can be used as valuable tools by a formulator who is involved in determining, improving, predicting, or describing the chemical stabilities of medicinal agents in pharmaceutical dosage forms.

The objective of this presentation is, as suggested by the chairmen of our seminar, to illustrate and emphasize in a positive manner how kinetic principles and knowledge of reaction mechanisms can be applied to the study of drug stability. It is not meant to be a comprehensive survey of the literature nor a review of chemical kinetics. In an attempt to meet the objective, a number of representative examples from the literature will be briefly discussed. These were not necessarily chosen on the basis of their relative significance but primarily because of a principle or principles illustrated. Principle and possible pharmaceutical application will be stressed without undo emphasis on the chemical aspects of a particular reacting system under discussion.

Many different pharmaceutical systems have been subjected to kinetic studies of one form or another. They have ranged, for example, from simple aqueous solutions of esters to quite complex multivitamin preparations. Because of this diversity of systems, it is difficult to formulate generalities. However, it is apparent that this approach can be of value in studying the stability of drugs in three general ways: by providing understandable and unequivocal methods for describing stabilities, by providing a sound starting point for formula design and processing, and by providing a theoretical basis for the prediction of stability. The latter topic will be the subject for the next presentation. This communication will deal with the former two topics.

Classical methods for describing the stabilities of drugs have been varied and ambiguous. Typical of this situation are the diffuse descriptions found in many of our pharmaceutical texts and references. Statements such as "quite stable," "fairly stable in alkaline media," "a reaction may occur on long storage," "stable for at least 25 hours," "buffered solutions are stable from one to two weeks," are found all too frequently and are, for practical purposes, quite useless.

The problems involved in defining stability have been discussed in detail by Schou (1).

A logical alternative to describing the stability of a given drug is to adequately characterize its instability. This alternative has certain advantages, since instability appears to be a much more general characteristic of drug molecules than stability. Furthermore instability can usually be described quite rigidly. Thus while stability may mean different things to different people, the term instability at least implies that degradative processes do occur at perceptible rates. It appears that the traditional method for describing the instability of a drug preparation, which usually consists of a table listing assay values obtained after storage at known temperatures for given periods of time, is gradually being superseded by more preferable methods. These methods are fundamentally based on the experimentally observed order of the degradative reaction or reactions responsible for the instability. Thus, for example, the rates of decomposition of vitamin B_{12} (2), aspirin in buffered solution (3), d-pantothenyl alcohol (4), thiamine (5), and other agents were reported to decompose in dosage form according to an observed first-order rate law:

$$\frac{dC}{dt} = -kC, \qquad (1)$$

Where

dC/dt = rate of decomposition
k = first-order rate constant
C = concentration

Similarly, other systems such as ergonovine maleate injections (6), penicillin G procaine suspensions (7), and suspensions of acylsalicylates (8) have been reported to decompose by zero-order rate laws:

$$dC/dt = -k', \qquad (2)$$

where k' is the zero-order rate constant. In many of these studies, the authors communicated the instability characteristics of the preparations by presenting in tabular form the experimentally determined first-order or zero-order rate constants at stated temperatures. Illustrative examples are shown in Tables 1 and 2. Here the order, rate constant, and temperature transmit the same story as a mass of raw data. Such a method has the advantages of being scientifically sound and universally understood; and it precisely provides a relatively complete description of the storage history. In addition, the information can be easily converted to a graphical representation of the study by use of the integrated forms of the rate equations as illustrated in Figs. 1 and 2.

TABLE 1—TABULATION OF FIRST ORDER RATE CONSTANTS FOR THE THERMAL DEGRADATION OF COMPONENTS IN LIQUID MULTIVITAMIN PREPARATIONS AT VARIOUS TEMPERATURES*

Component	Rate Constant x10 ²**		
	70°	60°	50°
Ascorbic Acid	5.78	2.07	0.707
Folic Acid	11.01	5.33	2.40
Vitamin B_{12}	3.32	1.308	0.408
Thiamine HCl	2.74	0.866	0.258
d-Pantothenyl alcohol	2.16	0.890	0.320
Vitamin A	2.62	1.38	-----

*Modified from: Garrett, E. R., J. Am. Parm. Assoc., Sci. Ed., 45, 171 (1956).
**Rate constant has units of $(2.303 \text{ days})^{-1}$.

TABLE 2—ERGONOVINE MALEATE ZERO-ORDER RATE CONSTANTS AT FIVE TEMPERATURES (U. S. P. FORMULATION)*

Temperature	Rate Constant x10^4	Range of Rate Constant x10^4
70°	230.0	190.0–280.0
60°	96.0	80.0–110.0
50°	23.0	19.0– 27.0
40°	12.0	9.3– 14.0
26.5°	1.8	1.3– 2.3

*Modified from: Moore, W. F., Drug Standards, 27, 187 (1959).

The term half-life ($t_{1/2}$), when applied pharmaceutically, indicates the time required for 50% decomposition of a drug is found with increasing frequency in the pharmaceutical literature to describe drug instability. This parameter conveys the same information as a rate constant because of the mathematical relationship between the two, for example,

$$\text{first-order} \quad t_{1/2} = 0.693/k, \qquad (3)$$

$$\text{zero-order} \quad t_{1/2} = 0.5C_0/k'. \qquad (4)$$

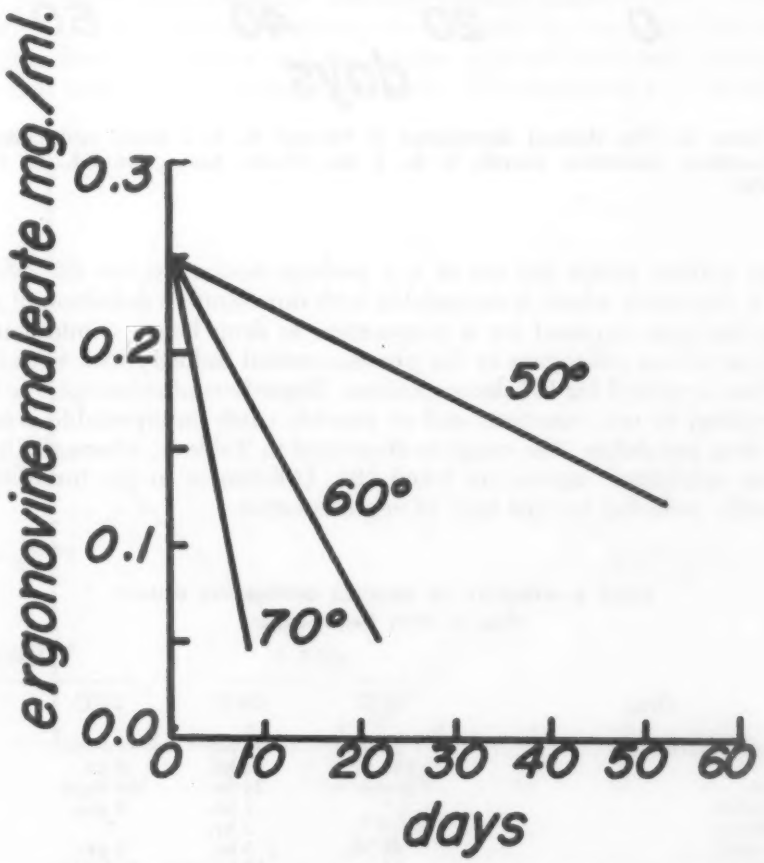

Figure 1.—The decomposition of ergonovine maleate solutions, U.S.P. formulation. Reference: Moore, W. E., Drug Standards, 27, 187 (1959).

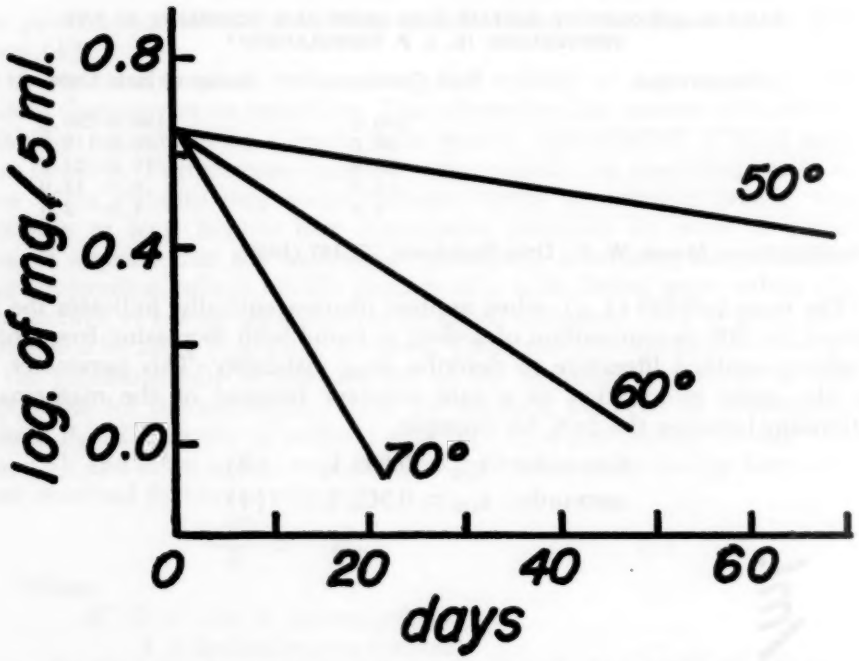

Figure 2.—The thermal degradation of Vitamin B_{12} in a liquid multivitamin preparation. Reference: Garrett, E. R., J. Am. Pharm. Assoc., Sci. Ed., 45, 171 (1956).

Some authors prefer the use of $t_{1/2}$, perhaps because it has the dimensions of time, a dimension which is compatible with our intuitive definition of stability as being the *time* required for a preparation to drop below a minimum assay value. Some of our colleagues in the pharmaceutical industry look with favor on $t_{0.1}$, the time required for 10% decomposition. Regardless of subscript, the t values can be related to rate constants and so provide easily interpretable representations of drug instability. The usage is illustrated in Table 3., where the half-lives of various ophthalmic agents are listed (9). Differences in the instabilities are quite vividly reflected by this type of representation.

TABLE 3—STABILITY OF SELECTED OPHTHALMIC DRUGS*
(Time for 50% Decomposition)

Drug	pH 5.0		pH 6.8	
	25°C	120°C	25°C	120°C
Procaine and Tetracaine	19 yr.	36 hr.	------	10 min.
Atropine	130 yr.	60 hr.	2 yr.	1 yr.
Pilocarpine	Stable	24 hr.	66 days	34 min.
Physostigmine	"	1 hr.	6 mo.	10 min.
Phenylephrine	"	2 hr.	?	?
Chlorobutanol	40 yr.	2.5 hr.	1 yr.	5 min.
Homatropine	14 yr.	10 hr.	0.4 yr.	10 min.

*Taken from: Riegelman, S., Husa's Pharmaceutical Dispensing, Mack Publishing Company, Easton, Pa., 1959, p. 266.

The use of rate constants or half-life values for defining the instabilities or stabilities of drug preparations is by no means a general practice, especially in the pharmaceutical industry. There is, however, a general awareness of the utility of the method. Concomitantly, there is a noticeable trend to modify conventional stability regimes to yield more extensive and more statistically effective assay data in an attempt to derive what is essentially more accurate and meaningful rate-constants.

Experimentation, preliminary to actual formulation studies, has been and is a necessary prerequisite to the development of a drug product possessing optimal stability. Many recent reports indicate that the inclusion into such a program of well-planned, short-ranged kinetic studies conducted under exaggerated conditions can be extremely useful. The philosophy of this approach was summarized by Higuchi *et al.* in their statement, "In essence, an approach to the problems of drug deterioration from the standpoint of chemical kinetics provides very useful clues to proper formulation based on actual knowledge of the character of the drug. In contrast, the purely empirical approach may overlook factors which are of substantial significance with respect to drug stability." (10)

The "pharmaceutical kineticist" and the chemical kineticist have in common the objective of experimentally defining the relationship that exists between the velocity of a chemical reaction and the various environmental and compositional variables that may occur in a reacting mixture. The dependency of reaction rate

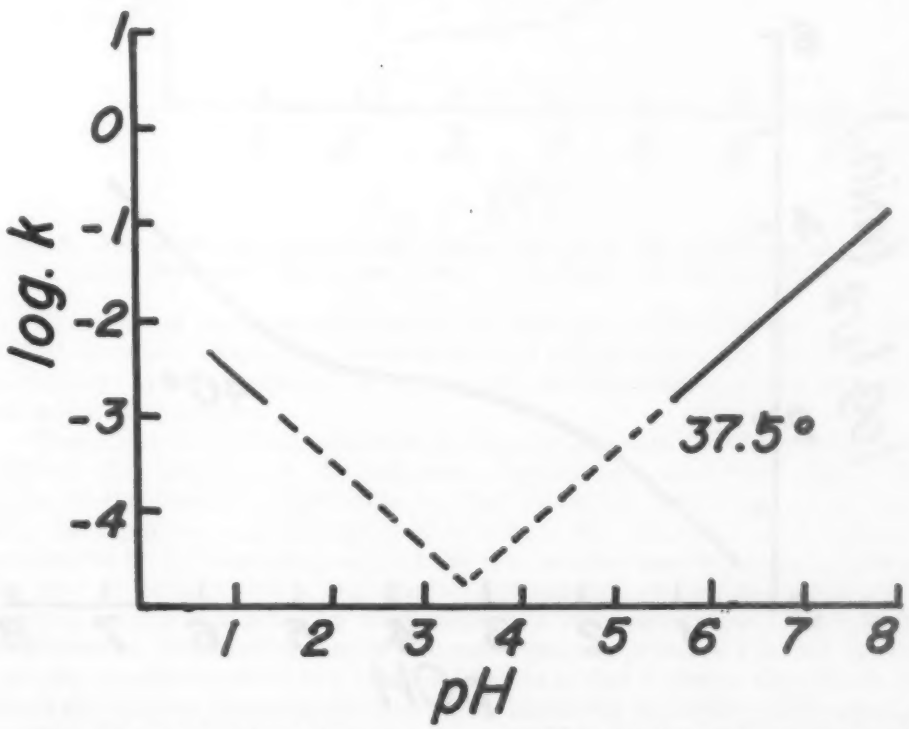

Figure 3.—The relationship between rate constant and pH for the decomposition of methantheline bromide. Reference: Nogami, H., et al, Bull. Pharm. (Japan), 6, 277 (1958).

on compositional variables such as the concentration of reactants and catalysts is conventionally expressed by the rate equation for the reaction. It is the rate equation that provides the chemist with clues as to the reaction mechanism. In addition, it provides him with a mathematical check as to the validity of a postulated mechanism. Similarly the rate equation is of value to a formulator, who may or may not be interested in reaction mechanisms, because it quantitatively pinpoints the extent to which the presence of such species as hydrogen ions, hydroxide ions, buffer components, oxygen, etc. may affect the rate at which a drug deteriorates in a product.

Rate equations can take many different forms depending on the mechanism of the reaction and the endurance of the investigator. The simplest type is the one term expression which was illustrated by equations (1) and (2). Complex one-term equations are encountered frequently as illustrated by that derived by Garrett (11) for the thermal degradation of fumagillin in the presence of air:

$$-dC/dt = \frac{2k_1k_2C^2(O_2)}{k_{-1} + k_2C} \qquad (5)$$

Expanded multi-term equations are the usual case and represent the type that can transmit a significant amount of information to a formulator. These usually take the form of:

$$-dC/dt = C\{k_{H_2O}(H_2O) + k_{OH^-}(OH^-) + k_{H^+}(H^+) + k_{HA}(HA) + k_{A^-}(A^-) + \ldots\} \qquad (6)$$

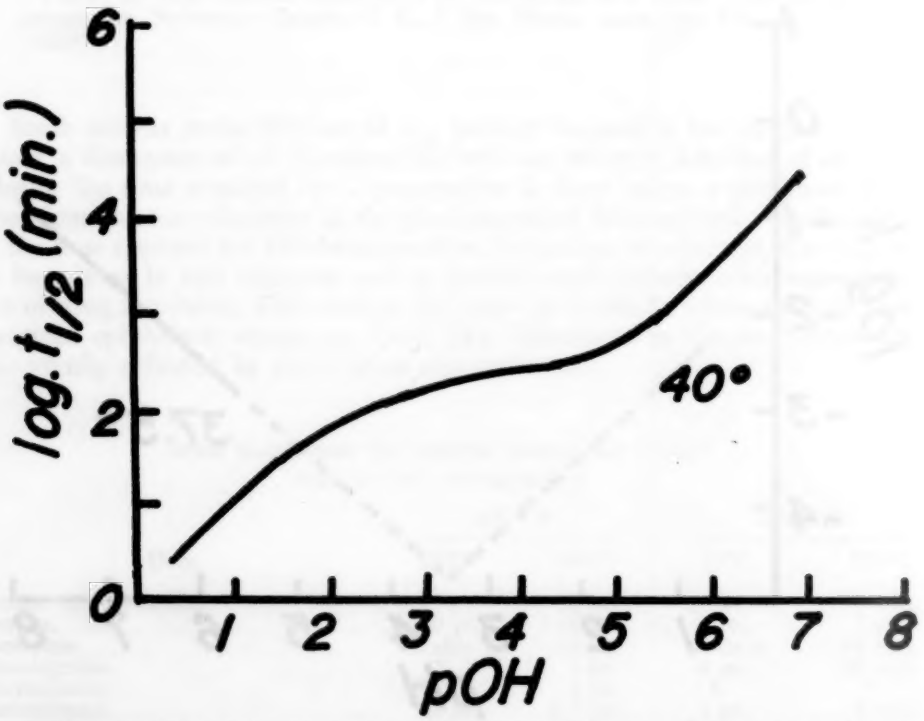

Figure 4.—The relationship between the half life of procaine and the hydroxide-ion concentration of the reaction mixture. Reference: Higuchi, T., Havinga, K., and Busse, L. W., J. Am. Pharm. Assoc., Sci. Ed. 39, 405 (1950).

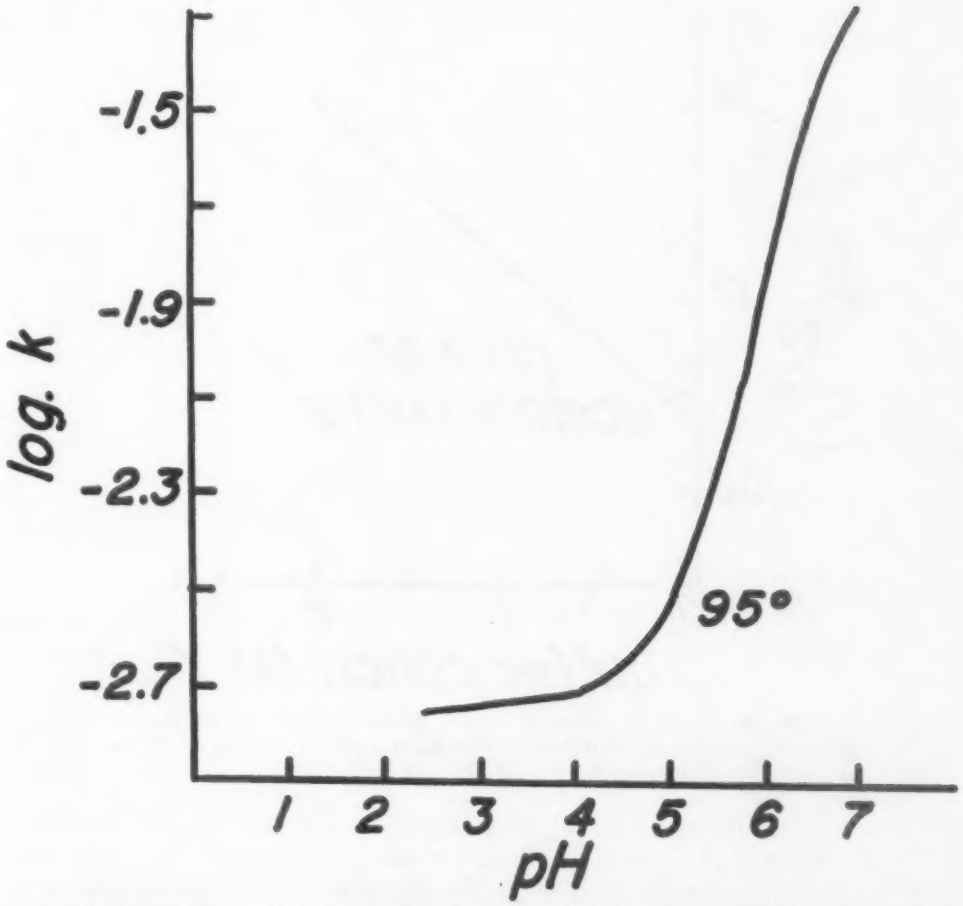

Figure 5.—The relationship between rate constant and pH for the degradation of morphine sulfate. Reference: Yeh, S., and Lach, J. L., J. Pharm. Sci., *50*, 35 (1961).

Equations of this type were found, for example, to describe the hydrolysis of local anesthetic esters (12), the hydrolysis of homatropine (13), the hydrolysis of atropine (14), the hydrolysis of aspirin (15), the degradation of morphine (16) and many other systems.

Regardless of its form, each term in the rate equation defines a degradative pathway that can involve the substrate. Furthermore, each term defines the nature of the reactants responsible for that particular degradative route. Similarly, the significance of each pathway relative to the overall rate of degradation is indicated by the numerical value of the rate constant specific for that pathway. The rate equation is thus a quantitative represenation of how the velocity of a chemical change is affected by components in a reaction mixture. Consequently, determination and examination of the rate equation provides a sound starting point for the development of a product formula in that it directs attention to the effects that various agents might have on the instability or stability of the agent in question. The same information, it is true, could be transmitted in other ways. The utility here, however, is in the precise, theoretically sound, quantitative manner in which the information is presented.

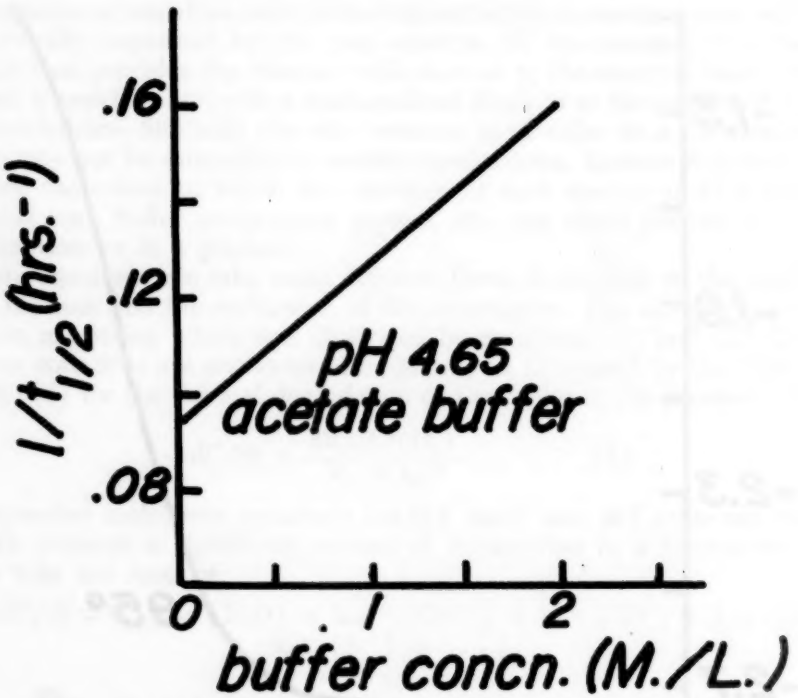

Figure 6.—Catalytic effect of acetate buffer on the rate of chloramphenicol degradation. Reference: Higuchi, T., Marcus, A. D., and Bias, C. D., J. Am. Pharm. Assoc., Sci. Ed., 43, 129 (1954).

The correct adjustment of pH, for example, is an important aspect in formulating a product with optimal stability. A considerable number of studies have been conducted to quantitatively define the dependency of drug deterioration on the concentation of hydrogen-ion and hydoxide-ion. As illustrated by numerous examples, the rate equation is a convenient method for depicting the results of such studies. For example, Nogami et al (17) demonstrated that the hydrolytic decomposition of methantheline bromide was described by the rate equation:

$$-d\,(M.B.)/dt = (M.B.)\,k_{H^+}\,(H^+) + k_{OH^-}\,(OH^-) + k_{H_2O}\,(H_2) \qquad (7)$$

Evaluation of the rate constants at 37.5° C. yielded a mathematical expression which described the pH profile of the degradation that is illustrated in Fig. 3. Similarly the pH dependency for the hydrolysis of procaine was defined by Higuchi et al (12) by the rate equation:

$$-d\,(\text{procaine})/dt = (\text{procaine})\,\frac{k_1(OH^-)^2}{K_b + (OH^-)} + \frac{k_2K_b\,(OH^-)}{K_b + (OH^-)} \qquad (8)$$

This equation mathematically described the rate of decomposition over a wide pH range as illustrated in Fig. 4. A study of the stability of morphine in aqueous solution was recently reported by Yeh and Lach (16). The relationship between stability and pH which is graphically depicted in Fig. 5 was described mathematically by the rate equation:

$$-d\,(\text{morphine})/dt = (\text{morphine})\,(O_2)\left\{\frac{k_1K_a}{K_a + (H+)} + \frac{k'_2\,(H^+)}{K_a + (H^+)}\right\} \qquad (9)$$

A limited number of kinetic studies have illustrated the possibility that various pharmaceutical adjuncts such as buffer components and antioxidants may have a deleterious effect on the stability of a medicinal agent. For example, Higuchi *et al.* demonstrated that the hydrolysis of chloromphenicol was catalyzed by general acids and bases such as acetic acid and acetate ion (10). Thus, in an acetate buffer, the hydrolysis was described by the equation:

$$-\mathrm{d}(\text{chloramphenicol})/\mathrm{dt} = (\text{chloramphenicol}) \{ k_{H_2O}(H_2O) + k_{H^+}(H^+) + k_{OH^-}(OH^-) + k_{HOAc}(HOAc) + k_{Ac^-}(Ac^-) \} \quad (10)$$

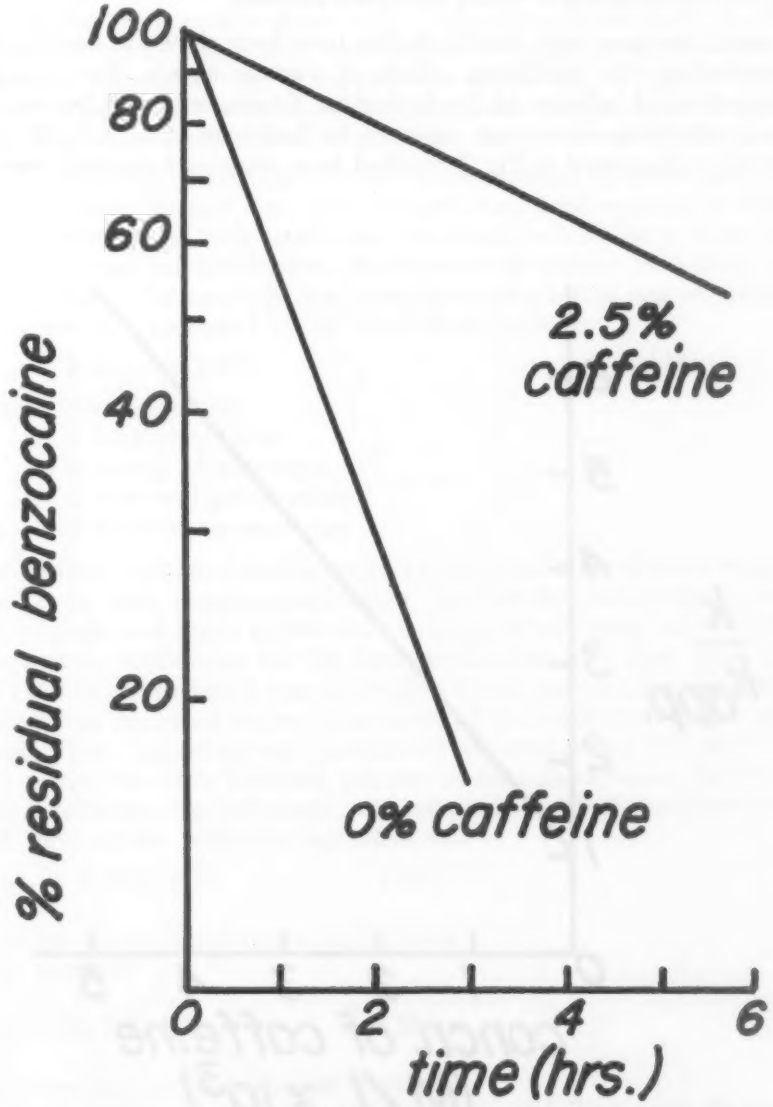

Figure 7.—The effect of caffeine on the rate of hydrolysis of benzocaine in alkaline media. Reference: Higuchi, T., and Lachman, L., J. Am. Pharm. Assoc., Sci. Ed., 44, 521 (1955).

The catalytic effect of acetate systems is illustrated in Fig. 6. In a similar manner Halwar (18) showed that the photolytic decomposition of riboflavin in aqueous solution is catalyzed by general acids and bases but not by hydrogen-ions according to the rate equation

$$-d\,(\text{riboflavin})/dt = (\text{riboflavin})\{\,k_o + k_A\,(A) + k_B\,(B)\,\} \qquad (11)$$

where the concentration terms represent the concentrations of general acids (A) such as acetic, formic, and pyridine hydrochloride, and general bases (B) such as acetate ion, formate ion, and pyridine and k_o represents the specific rate constant for the spontaneous or water catalyzed reaction

In much the same way, kinetic studies have been shown to be very effective in demonstrating the stabilizing effects of various agents. For example, the stabilizing effect of caffeine on the hydrolytic decomposition of benzocaine and other local anesthetic esters was reported by Lachman *et al.* (19, 20, 21) The effect which is illustrated in Fig. 7 resulted from complex formation between the

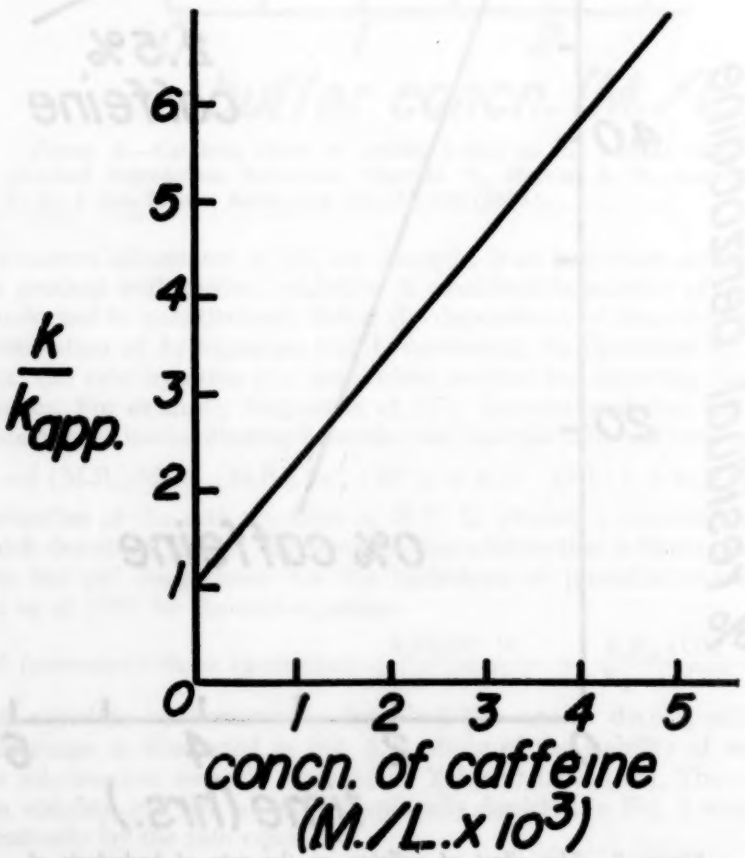

Figure 8.—The effect of caffeine on the photolytic decomposition of riboflavin. Reference: Guttman, D., Unpublished data.

ester and caffeine and a subsequent decrease in the thermodynamic activity of the ester. Thus the rate equation normally defining the rate of hydrolysis:

$$-\text{d (benzocaine)}/\text{dt} = \text{k (benzocaine) (OH}^-\text{)} \qquad (12)$$

is modified in the presence of caffeine to yield

$$-\text{d (benzocaine)}/\text{dt} = \frac{\text{k(benzocaine) (OH}^-\text{)}}{1 + \text{K}_s\text{ (caffeine)}} \qquad (13)$$

where K_s is the stability constant characterizing the complexing equilibrium. The rate of the light catalyzed decomposition of riboflavin was also shown to be decreased in the presence of caffeine (22). Typical results are shown in Fig. 8. It is seen that the stabilizing effect, measured by the ratio of the rate constant in the absence of caffeine to that in the presence of caffeine, is linearly dependent on the concentration of the stabilizer. Such behavior suggests that complexation of the reacting molecule is a likely explanation for the observed effect.

The dependency of reaction rate on environmental variables such as temperature, dielectric constant, and ionic strength have been extensively studied by chemical kineticists and well established relationships have been found to exist. Application of such relationships to pharmaceutical systems have been made in a number of cases. For example, the dependency of reaction rate on temperature which is classically expressed by the Arrhenius equation:

$$k = A\exp{-E/RT} \qquad (14)$$

where k = rate constant
A = frequency factor
E = energy of activation
R = universal gas constant
T = absolute temperature,

has been applied with considerable success to the prediction of room temperature stabilities from high temperature studies. Another interesting application was made by Higuchi and Busse to provide a criterion for choosing between high and low temperature techniques for the heat sterilization of a heat labile pharmaceutical (23). They reasoned that although a lower temperature might be easier on the drug, the increased contact time required for sterilization might offset this advantage. Their reasoning was quantitated by considering the effect of temperature on the two rates involved, the rate of drug inactivation and the rate of bacterial inactivation. In both cases, the temperature effect was expressed by a modified form of the Arrhenius equation, *i.e.:*

$$\text{In } t_{1/2} = E_1/RT + C, \qquad (15)$$

where
E_1 = the energy of activation for the drug
C = constant,

and

$$\text{In } t_d = E_s/RT + K, \qquad (16)$$

where
t_d = the time necessary for sterilization
E_s = the energy of activation characteristic of killing most thermally resistant organisms.
K = constant

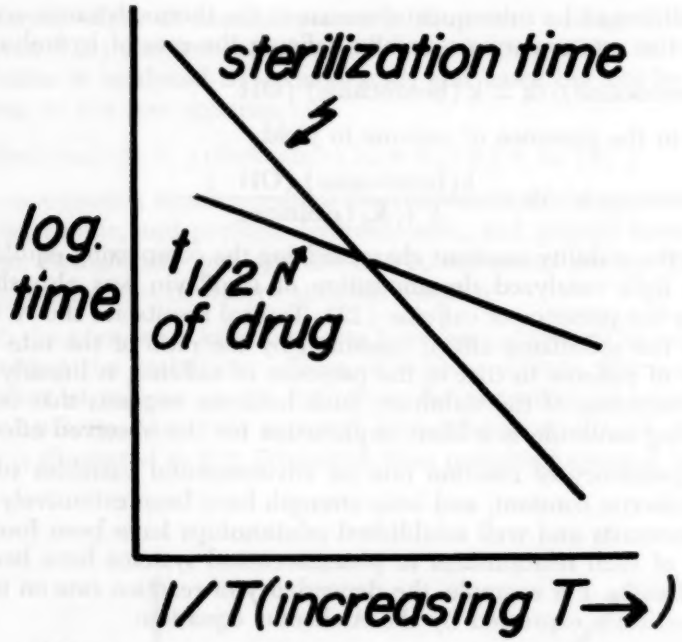

Figure 9.—General criterion for choosing high or low temperatures for sterilizing heat-sensitive pharmaceuticals. Reference: Higuchi, T., and Busse, L. W., J. Am. Pharm. Assoc., Sci. Ed., 39, 411 (1950).

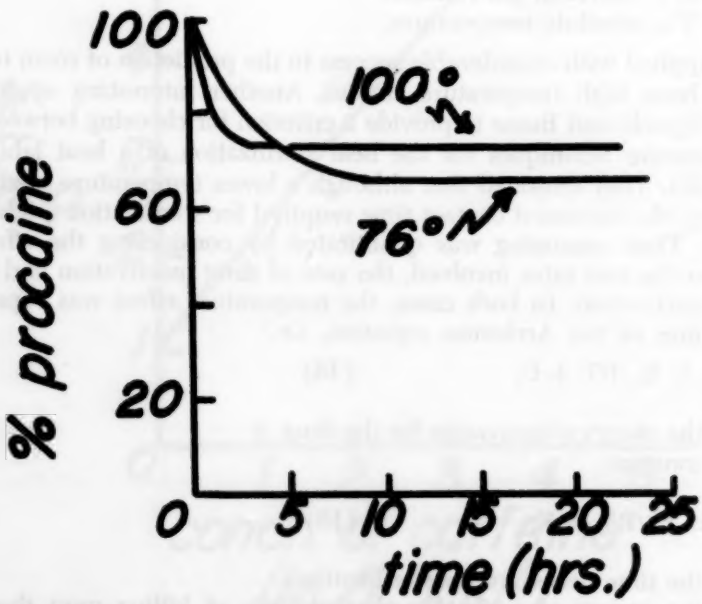

Figure 10.—The disappearance of procaine from solutions containing procaine (5 mg./ml.) and glucose (50 mg./ml.). Reference: Ikeda, K., Bull. Pharm. (Japan), 5, 101 (1957).

These two relationships were graphically depicted as shown in Fig. 9. It can be seen that if the sterilization line has a sharper slope than the line representing the decomposition reaction then, high temperature, low contact time manifests itself in less drug decomposition than low temperature, high contact time conditions. Since the relative slopes of the lines depend directly on the magnitude of the respective activation energies, the application can be of general utility and requires only a knowledge of E_d and E_s.

The temperature dependency of the reaction forming procaine-N-glucoside in injectables containing procaine and glucose was studied in an elegant manner by Ikeda (24). The kinetic picture in this system was complicated by the mechanism of the reaction in which the reverse reaction occurred at a perceptible rate. Illustrative results, as depicted by the author, are shown in Fig. 10. He showed, in this manner, that although the rate of disappearance of procaine from the preparation increased with an increase in temperature, the amount of procaine present at equilibrium was greater at higher temperatures. The study yielded the practical conclusion that refrigerator storage of the product is unwise and that, unless the product is used shortly after processing, heat sterilization could be used in place of sterilization by aseptic manipulation.

Partial or complete change in a solvent system is often attempted as a possible method for improving the stability characteristics of a pharmaceutical solution. At least two recent studies have shown that a knowledge of reaction mechanism can provide a theoretical basis for the utility or undesirability of such a manipulation. Marcus and Taraszka, for example, found that the rate of the acid-catalyzed hydrolytic decomposition of chloramphenicol was greater in propylene glycol-water systems than in water alone (25). The effect was explained as being due to a mechanism which involved the reaction between a proton and an uncharged form of the antibiotic. The observed effect would therefore be anticipated on the basis of the theoretical considerations of Amis who derived the inverse relationship between the dielectric constant of the medium and the rate of a dipole-positive ion reaction (26). Similarly Ikeda demonstrated that the increased stability of hexobarbital in hydro-alcoholic solutions containing ethanol, ethylene glycol, or glycerol could be theoretically rationalized by considering the decrease in the dielectric constant of the systems which resulted from the addition of the alcohol (27, 28). There the mechanism involved the reaction of negatively charged species, and it was shown that the magnitude of the stabilization could be accounted for on a sound theoretical basis

The examples which have been cited and many other similar studies are evidence that a great deal of important and useful information can be derived in a relatively short period of time by utilization of a kinetic approach to the problems of drug stability. The practical utility of such an approach should not be minimized in spite of the fact that most of the interest and activity has been centered in academic institutions. It is indeed quite conceivable that kinetic studies will, someday, be routine undertakings in product research and developmental areas as a natural prelude to actual formulation studies.

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THE USE OF STABILITY DATA IN PREDICTING STABILITY

JAMES W. CONINE

What is the value of being able to predict quantitatively the shelf life of a pharmaceutical preparation? The best answer is probably this, that products can be placed on the market in a much shorter time, if predictions can be used in place of actual long-term shelf life data. Also, the necessity for dating products can be determined and the proper dating period estimated. In addition, special storage requirements may be determined before the product is released for sale.

Is stability information worth what it costs? How much stability information can we afford? The answers to these questions must be qualified. Since a certain amount of stability data is always necessary in the development of any new product, the data should be collected in such a way that adequate information for the prediction of shelf life can be obtained. Actual data are more reliable than predictions, but it is generally undesirable to wait the length of time required to collect adequate room temperature data. The more assays on a product, the more accurate is the prediction, but high degrees of certainty can be bought only at high prices.

Predictions Obtained at a Single Temperature

It is desirable to determine the order of the reaction to establish the theoretical curve from which the stability predictions will be made. When this is done the experimental values obtained from the study can be fitted to this curve. The extension of the curve can then be used to estimate the amount of the product remaining at any later time.

The reaction order in pharmaceutical solutions is usually first order or higher. In suspensions or emulsions, zero order reactions are often observed.

$$\text{zero order } \frac{dx}{dt} = k_0, \quad \text{1st order } \frac{dx}{dt} = k_1 X, \quad \text{2nd order } \frac{dx}{dt} = k_2 X\,Y \qquad (1)$$

Zero order reactions are a result of a small fixed amount of the reactant decomposing, while most of it is not able to react as rapidly. This may be the result of a low solubility of the reactant in the reaction medium. In first order reactions the reactant decomposes at a rate dependent upon its concentration in the reaction medium. Second order reactions depend upon the concentration of the reactant and some other ingredient which is present in such a limited quantity that its concentration changes drastically as the reaction proceeds. Higher orders of reactions are uncommon.

When only two points are available, any curve can be fitted to pass through them. As the number of assays increase, the order of the reaction should become more evident. Zero and first order reactions can be plotted as straight lines. In addition to a graphical solution, mathematical methods are available to estimate the best straight line passing through the data. One of these methods is the commonly used "Method of Least Squares." (12)

y = Assay value which plots as straight line, either actual value or log of value
t = Time
k = Reaction rate constant
n = Number of assays
V = Variance

$$k = \frac{\Sigma y(t-\bar{t})}{\Sigma(t-\bar{t})^2} \quad (1) \qquad k = \frac{\Sigma(ty) - \frac{(\Sigma t)(\Sigma y)}{n}}{\Sigma t^2 - \frac{\Sigma^2 t}{n}} \quad (2)$$

The extension of this straight line will give the best estimate for the amount of active ingredient remaining in the product at some future date.

Only one straight line can be drawn when two assays are available, and therefore there is insufficient data for any comparisons to be made. As the number of assays is increased, more data are available and the estimated rate of the reaction should be closer to the true rate of reaction, and also more comparisons are available to allow a more accurate estimate of the reliability of the rate estimate from all the assays. The variance of a single assay may be determined as follows: (The formula for computer use follows the simplified form.)

$$V_y = \frac{\Sigma(y-\bar{y})^2 - \frac{(\Sigma y(t-\bar{t}))^2}{\Sigma(t-\bar{t})^2}}{n-2} \quad (3)$$

$$V_y = \frac{\Sigma y^2 - \frac{\Sigma^2 y}{n} - \frac{\left(\Sigma yt - \frac{\Sigma y \Sigma t}{n}\right)^2}{\Sigma t^2 - \frac{\Sigma^2 t}{n}}}{n-2} \quad (4)$$

The variance of the rate, k, is determined from the variance of y.

$$V_k = \frac{Vy}{\Sigma(t-\bar{t})^2} = \frac{\Sigma(y-\bar{y})^2 - \frac{(\Sigma y(t-\bar{t}))^2}{\Sigma(t-\bar{t})^2}}{(n-2)\quad \Sigma(t-\bar{t})^2} \quad (5)$$

$$V_k = \frac{\Sigma y^2 - \frac{\Sigma^2 y}{n} - \frac{\left(\Sigma yt - \frac{\Sigma y \Sigma t}{n}\right)^2}{\Sigma t^2 - \frac{\Sigma^2 t}{n}}}{(n-2)\left(\Sigma t^2 - \frac{\Sigma^2 t}{n}\right)} \quad (6)$$

The variance of the average value of y, $\bar{y}$, is

$$V_{\bar{y}} = \frac{1}{n} V_y \quad (7)$$

The equation for the best straight line that can be obtained from the data is

$$Y_1 = \overline{y} + k\,(t_1 - \overline{t}) \tag{8}$$

where Y_1 is the theoretical or predicted value of y (Figure 1). The variance of Y_1 (the prediction) is—

$$V_{Y_1} = V_y + (t_1 - \overline{t})^2 V_k \tag{9}$$

$$V_{Y_1} = \left(\frac{1}{n} + \frac{(t_1 - \overline{t})^2}{\Sigma(t - \overline{t})^2}\right) V_y \tag{10}$$

The ways to decrease V_{Y_1} which can be seen from equation (10) are to increase n and make $(t_1 - \overline{t})$ as small as possible. In addition, if a prediction representative of a multiple assay is to be made, then the division of V_{Y_1} by n′ (3), the number of assays at Y_1, will reduce the variance of the estimate. This will not be as satisfactory as it might seem unless care is taken to consider *all* the variables included in obtaining Y_1. In addition, single sided distribution may

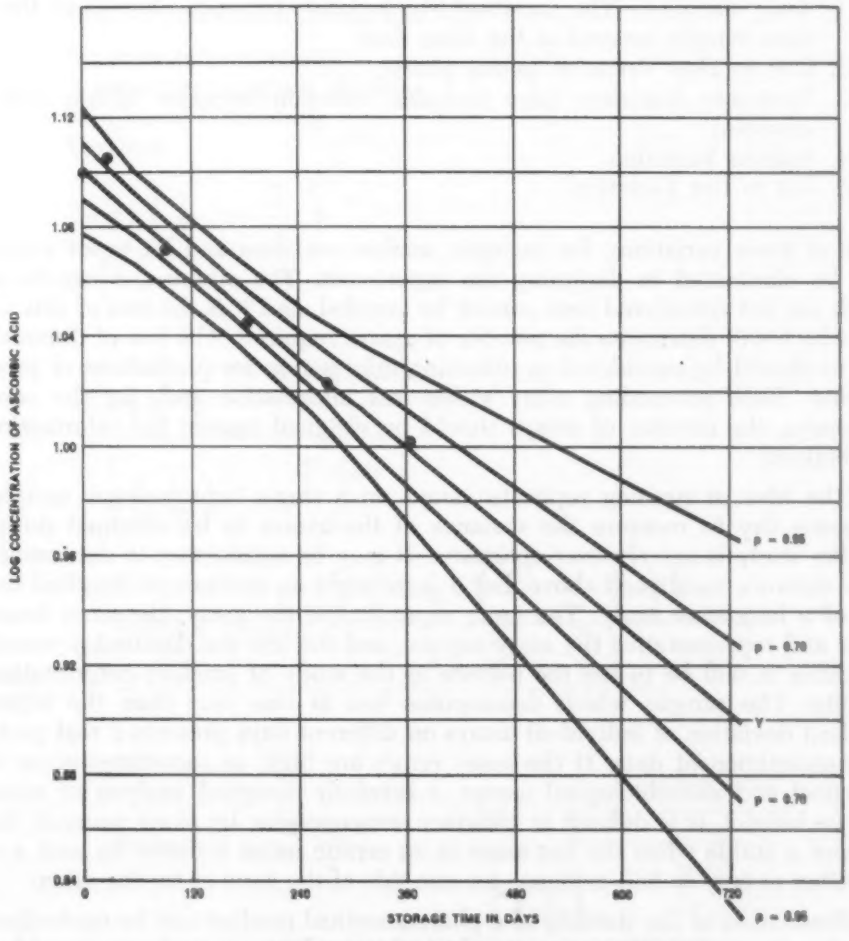

Fig. 1—PREDICTION OF ASCORBIC ACID STABILITY

be considered here, if the estimate of probability s to exclude only data falling below $Y_1 - ts$ rather than outside $Y_1 \pm ts$.

$$s = \sqrt{V_{Y_1}} \tag{11}$$

Figure 1 illustrates and summarizes the prediction of stability from kinetic or stability data. When the data are obtained in a manner to make $(t - \bar{t})$ the most favorable for minimizing V_{Y_1}, then the least is known about the velocity constant, k. As can be seen, V_y and V_k are related and dependent upon this same data. As n increases, V_y and V_k will tend to approach more closely the true variance of the universe, σ_k^2. The range of deviation from Y is determined by the student "t" and is dependent also upon the size of n. As n increases, "t" decreases and, at an infinite number of samples, asymptotically approaches a minimum value. This can be seen by examination of the "t" table.

How many assays should be obtained to get the best results? This depends upon the variables which are involved in the assay method and the stability study. Some of the more prominent ones are listed below:

1. Assay variation—The variation which occurs between aliquots of the same sample assayed at the same time.
2. Day to Day Variation (moon phase)
3. Container Variation (also includes variation between tablets and capsules)
4. Analyst Variation
5. Lot to Lot Variation

Some of these variations, for example, analyst variation and lot to lot variation, may be eliminated in designing the experiment. The others and maybe more which are not considered here cannot be avoided, and it is the size of this variation which will determine the number of assays required. The law of diminishing returns should be considered in obtaining information for predictions of product stability. Each succeeding assay yields less information and, for the sake of economics, the number of assays should be weighed against the information to be obtained.

The idea of running replicate assays on a single homogeneous sample on the same day to measure the variance of the assays to be obtained during a stability study is naively over-optimistic. It may be satisfactory to determine the assay variance mentioned above, but it is too tight an estimate of standard deviation of a long-term study. The more reproducible the assay, the more homogeneous and representative the assay sample, and the less the day-to-day variation, the easier it will be to see the pattern of the study of product deterioration or stability. The sample which decomposes less in one year than the expected standard deviation of individual assays on different days presents a real problem in interpretation of data. If the assay errors are high, as sometimes occur with biological and microbiological assays, a carefully designed analysis of variance may be helpful. It is difficult to convince someone else, let alone yourself, that a product is stable when the last assay in an erratic series is down. In such a case, it is often as easy to find evidence for one side of the issue as for the other.

Predictions of the stability of a pharmaceutical product can be made directly from kinetic studies. The range in which this prediction may be expected to fall

depends directly on the day-to-day assay variation and on the time interval between the average value of the data and the prediction, and, inversely, on the number of assays.

Predictions Made from Data Obtained at Several Temperatures

The stability of a product at one temperature can be estimated from the data obtained from stability studies at several other temperatures (4–9). This is done by utilizing the Arrhenius relationship between reaction rate and absolute temperature. The usefulness of this equation is dependent upon having a constant energy of activation, E_a, over the range of temperatures studied. In a sense, when data obtained at several temperatures are used, the result is no longer an extrapolation but an interpolation of data, since at higher temperatures the decomposition has proceeded beyond that expected for the usual shelf life of a product at room temperature. The equations are of the same sort used to determine the slope of relationship between the concentration of compound and age of the sample.

S = Slope of relationship of $\log k$ to $\frac{1}{T}$

k = Reaction rate constant
T = Temperature degrees absolute
n = Number of k's in study
V = Variance

$$S = \frac{\Sigma \log k \left(\frac{1}{T} - \frac{\overline{1}}{T} \right)}{\Sigma \left(\frac{1}{T} - \frac{\overline{1}}{T} \right)^2} \tag{12}$$

$$S = \frac{\Sigma(\log k)\frac{1}{T} - \frac{\Sigma(\log k)\Sigma\frac{1}{T}}{n}}{\Sigma\left(\frac{\overline{1}}{T}\right)^2 - \frac{\Sigma^2\frac{1}{T}}{n}} \tag{13}$$

$$V_{\log k} = \frac{\Sigma(\log k - \overline{\log k})^2 - \frac{\left(\Sigma \log k \left(\frac{1}{T} - \frac{\overline{1}}{T} \right)\right)^2}{\Sigma \left(\frac{1}{T} - \frac{\overline{1}}{T} \right)^2}}{n-2} \tag{14}$$

$$V_{\log k} = \frac{\Sigma(\log k)^2 - \frac{\Sigma^2 \log k}{n} - \frac{\Sigma(\log k)\frac{1}{T} - \frac{\Sigma \log k \, \Sigma \frac{1}{T}}{n}}{\Sigma\left(\frac{1}{T}\right)^2 - \frac{\Sigma^2\frac{1}{T}}{n}}}{n-2} \tag{15}$$

$$V_S = \frac{V_{\log k}}{\Sigma\left(\frac{1}{T} - \frac{\bar{1}}{T}\right)^2} \tag{16}$$

$$V_S = \frac{V_{\log k}}{\Sigma\left(\frac{1}{T}\right)^2 - \frac{\Sigma^2 \frac{1}{T}}{n}} \tag{17}$$

$$\log k_1 = \log k + S\left(\frac{1}{T_1} - \frac{\bar{1}}{T}\right) \tag{18}$$

$$V_{\log k_1} = V_{\log k} + \left(\frac{1}{T_1} - \frac{\bar{1}}{T}\right)^2 V_S \tag{19}$$

$$V_{\log k_1} = V_{\log k}\left(\frac{1}{n} + \frac{\left(\frac{1}{T_1} - \frac{\bar{1}}{T}\right)^2}{\Sigma\left(\frac{1}{T} - \frac{\bar{1}}{T}\right)^2}\right) \tag{20}$$

The graphical solution of the problem may be a little easier to see. The standard deviation of each value of log k can be represented graphically (8). The prediction $V_{\log k}$ is then the answer to be expected having the same number of points on the log k prediction as on the log k values used in the prediction. Log k may be plotted against $\frac{1}{T}$ or as log time when a certain percent of initial assay remains against $\frac{1}{T}$. The latter approach can be used in circumstances such as development of bitterness in sitosterols (Figure 2) where no quantitative data are available. This approach has been used to determine shelf lives of vitamins (3).

With studies of this sort, the greatest error is in overestimating the reliability of the prediction rather than a reluctance to accept the prediction. Statistical methods are not intended as a substitute for common sense and good judgment. Their purpose is to give a valid basis of mathematical probability for the evaluation of product stability. Statistical studies are designed to evaluate only the data collected in the particular study. In the human mind a recall of data and experience both relevant and irrelevant occurs. We are failing to use our common sense when we discount pertinent data from a relevant study and replace it with data of a possible irrelevant nature dredged up somewhere out of the depths of past experience.

Second Order Reactions

Reactions of the second order are dependent upon the concentration of two ingredients, one usually being the active ingredient. Conditions are such that a reaction which is normally a zero or first order becomes a second order, because one of the ingredients which reacts with the active ingredient is present in such a limited amount that its increase or decrease is reflected in the changing rate of the reaction. In liquid multiple vitamin formulations, various factors, such as

hydrolysis, light, and oxidation, may affect the different vitamins in differing ways. The effects are additive. When the effect is limited, it results in a second order decomposition for its share of the reaction. It is possible that the over-all rate of the reaction may become quite complex. The main reactions occurring in multiple vitamin preparations protected from air are slow zero or first order reactions (Figure 3). When considerable air is present, the reaction becomes very rapid second order. If the amount of air were unlimited, the reaction would probably approach a zero or first order pattern. A comparison, at various tem-

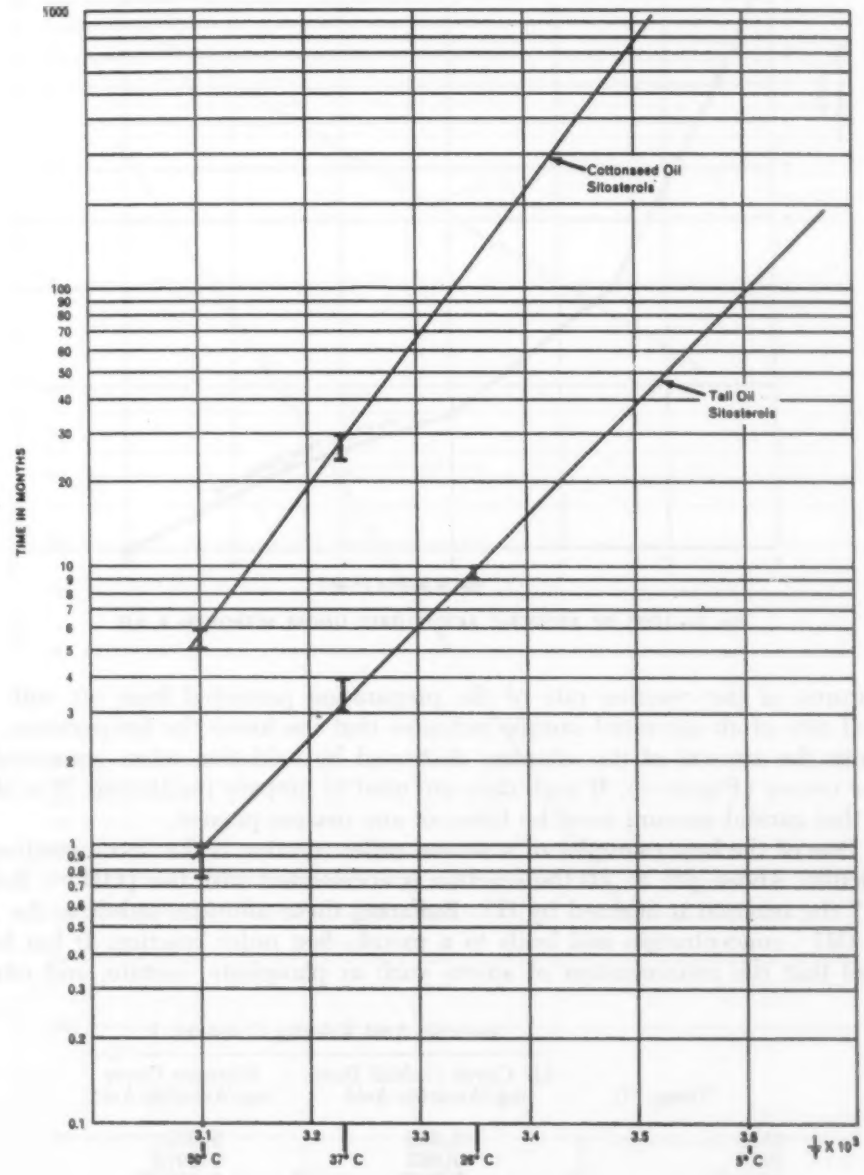

Fig. 2—DEVELOPMENT OF BITTER TASTE IN β SITOSTEROLS

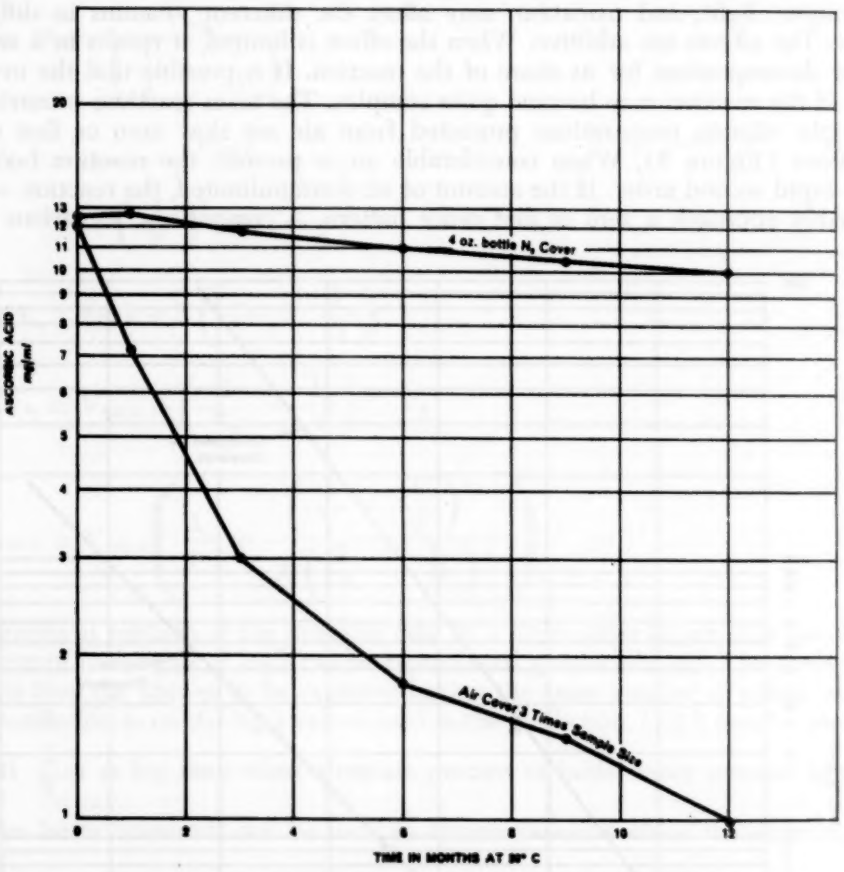

Fig. 3—LOSS OF ASCORBIC ACID STORED UNDER NITROGEN & AIR

peratures, of the reaction rate of the preparation protected from air with the initial rate of air-saturated sample indicates that the lower the temperature, the greater the amount of the vitamins destroyed by oxidation when compared to other causes (Figure 4). If such data are used to prepare predictions, it is obvious that careful account must be taken of any oxygen present.

One of the best examples of a second order reaction is the decomposition of penicillin. Above pH = 7.0 the reaction is accelerated with the $(OH)^-$. Below pH 7 the reaction is affected by H^+. Buffering these solutions stabilizes the H^+ and OH^- concentration and leads to a pseudo first order reaction. It has been stated that the concentration of anions such as phosphate, acetate, and citrate

	Ascorbic Acid Velocity Constant, k	
Temp. °C.	Air Cover (Initial Rate) mg/Ascorbic Acid	Nitrogen Cover mg/Ascorbic Acid
65	0.095	0.035
50	0.060	0.0073
37	0.0267	0.00246
26	0.0186	0.00060

also affect the rate of the reaction (10). Predictions can be attempted with second order kinetics if both components can be accurately measured. However, the fact that a second order reaction occurs suggests that a slower zero or first order reaction can be achieved by one of the following methods:

1. Removal of the agent which accelerates the reaction rate.
2. Addition of an ingredient to stabilize or decrease the reaction rate.

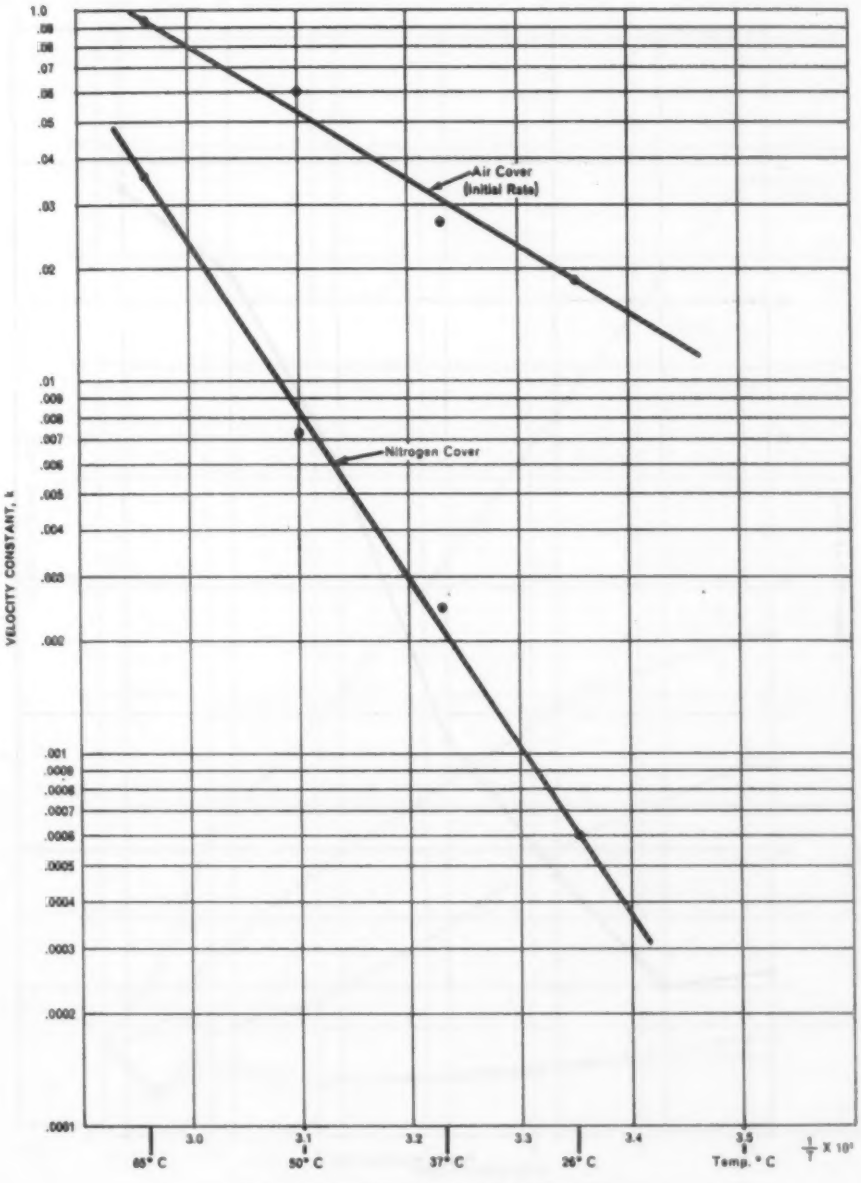

Fig. 4—ASCORBIC ACID ARRHENIUS PLOT

When confronted with a second order reaction, it should be more worthwhile to expend one's effects in determining ways to reduce the reaction rate to a slower zero or first order process than to continue efforts to precisely predict a second order curve.

Decomposition as Indicated by Color Development

The fading of a dye under the influence of light, heat, or some other uniform influence generally follows a first order reaction. Color development in pharmaceutical preparations usually follows another pattern. If Compound A decom-

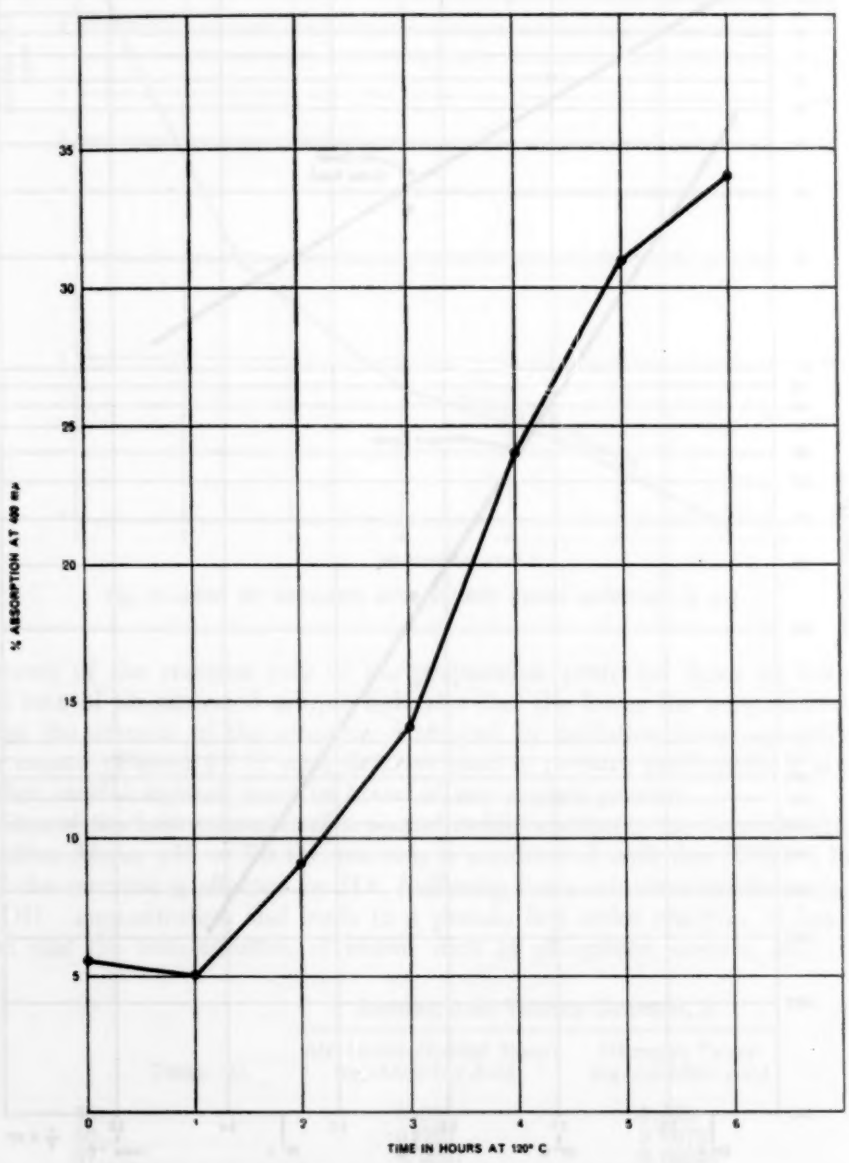

Fig. 5—COLOR DEVELOPMENT IN CITRUS PECTIN SOLUTION

poses to a colored Compound B, the product B increases with time according to equation

$$A \xrightarrow{k} B$$

A somewhat more complex situation results when simultaneous reactions occur (11).

$$A \xrightarrow{k_1} B \qquad B \xrightarrow{k_2} C$$

Data on the browning of pectin solution at pH 3.5 (color intensity at 400 mμ) seem to follow such a simultaneous equation (Figure 5). The evaluation of k

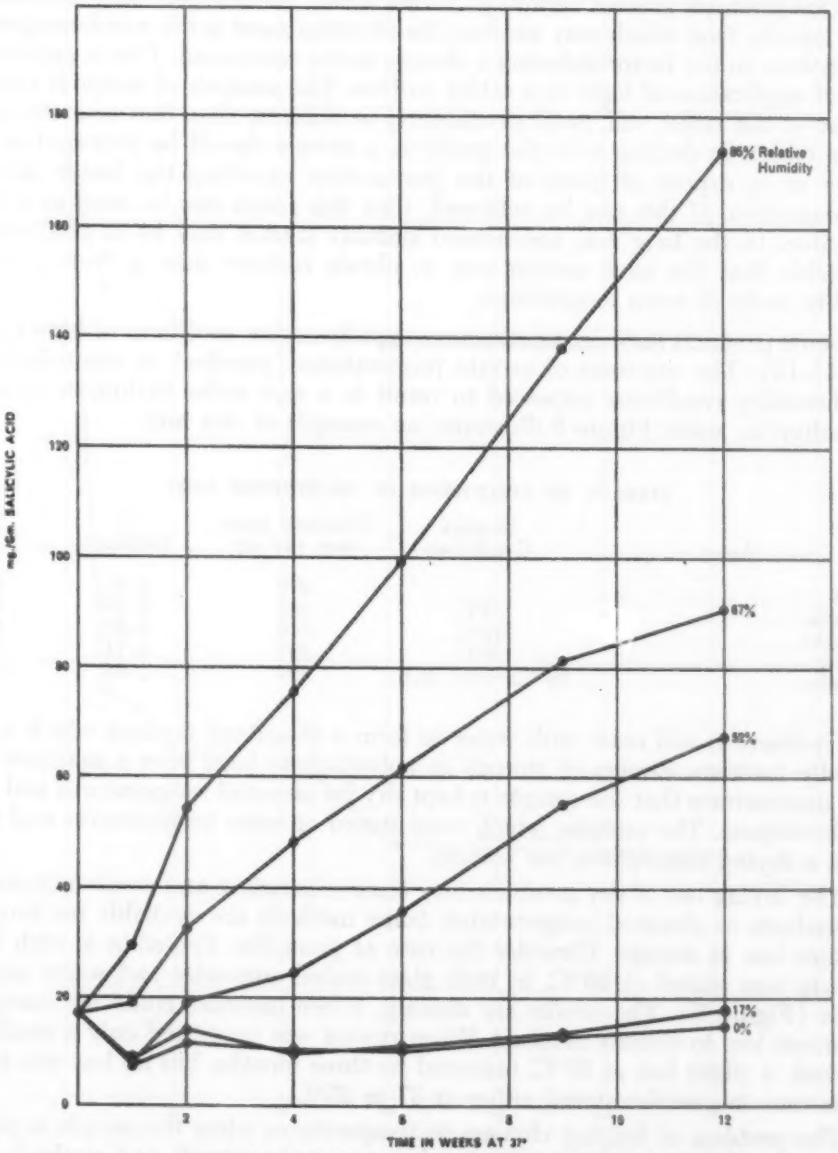

Fig. 6—FORMATION OF SALICYLIC ACID FROM ASPIRIN IN POWDER

values is essential for the solution of such an equation. k_1 may be determined from the disappearance of Compound A. If Compound B is known, then the concentration of Compound C may be predicted. As likely as not we will have little knowledge of the nature of B. Since darkening and discoloration of pharmaceuticals are problems of serious importance, the ability to predict the appearance of these objectionable occurrences will be of great value. As with second order reactions, the elimination of discoloration is more desirable than its accurate prediction.

The Problem of Dry Products

Dry products present certain problems which are not generally encountered with liquids. One which may confuse the situation most is the non-homogenicity of exposure to the factor inducing a change in the compound. This is particularly true of application of light to a tablet surface. The analysis of material near the surface of the tablet will, in all probability, be different than that near the center of the tablet. In dealing with this problem, a sample should be prepared in such a way as to expose all parts of the preparation equalling the factor affecting decomposition. If this can be achieved, then this result can be used as a limiting value. In the long run, accelerated stability studies may be so confusing or unreliable that the most certain way to obtain realistic data is from a simple stability study at room temperature.

Some products may deteriorate more rapidly under conditions of high humidity (12–13). The exposure of aspirin preparations (powder) to controlled relative humidity conditions appeared to result in a zero order hydrolysis to acetic and salicyclic acids. Figure 6 illustrates an example of this sort.

STABILITY OF CYCLOSERINE IN POLYETHYLENE BAGS

Age	Storage Conditions	Chemical Assay mcg. per mg.	% Moisture	% Dimer
Initial	-----	979	0.41	0.63
3 months	50°C.	987	0.29	0.58
3 months	37°C.	970	0.35	0.56
3 months	26°C.	937	0.71	2.28
3 months	26°C.—85% R.H.	804	1.64	14.1

Cycloserine will react with water to form a dimerized product which is biologically inactive. Results of storage in polyethylene bags (not a moisture barrier) demonstrate that the sample is kept dry by elevated temperatures and does not decompose. The samples which were stored at room temperatures and were not in a drying atmosphere lost activity.

The drying out of dry products may remove moisture and result in more stable products at elevated temperatures. Some methods are available for avoiding moisture loss in storage. Consider the case of penicillin. Penicillin V with 1.14% moisture was stored at 65°C. in both glass sealed ampoules and screw capped bottles (Figure 7). The results are striking. When moisture could not escape, a 40 percent loss in activity resulted. When drying was permitted only a small loss occurred. A slight loss at 50°C. occurred by three months, but no loss was noted at this time in samples stored either at 37 or 25°C.

The problem of lagging changes in temperatures when the sample is placed in or removed from a storage oven has been treated in detail, and methods have

been suggested for estimating this variable (14, 15). Products which change in physical form (crystal structure) may not be easily handled by a prediction of stability which does not take this factor into account.

Factorial Design of Experiments

Experimental design may be of value in the determination of how much certain ingredients and interactions of ingredients affect the stability of a pharmaceutical preparation. Many experimental designs are available and may be

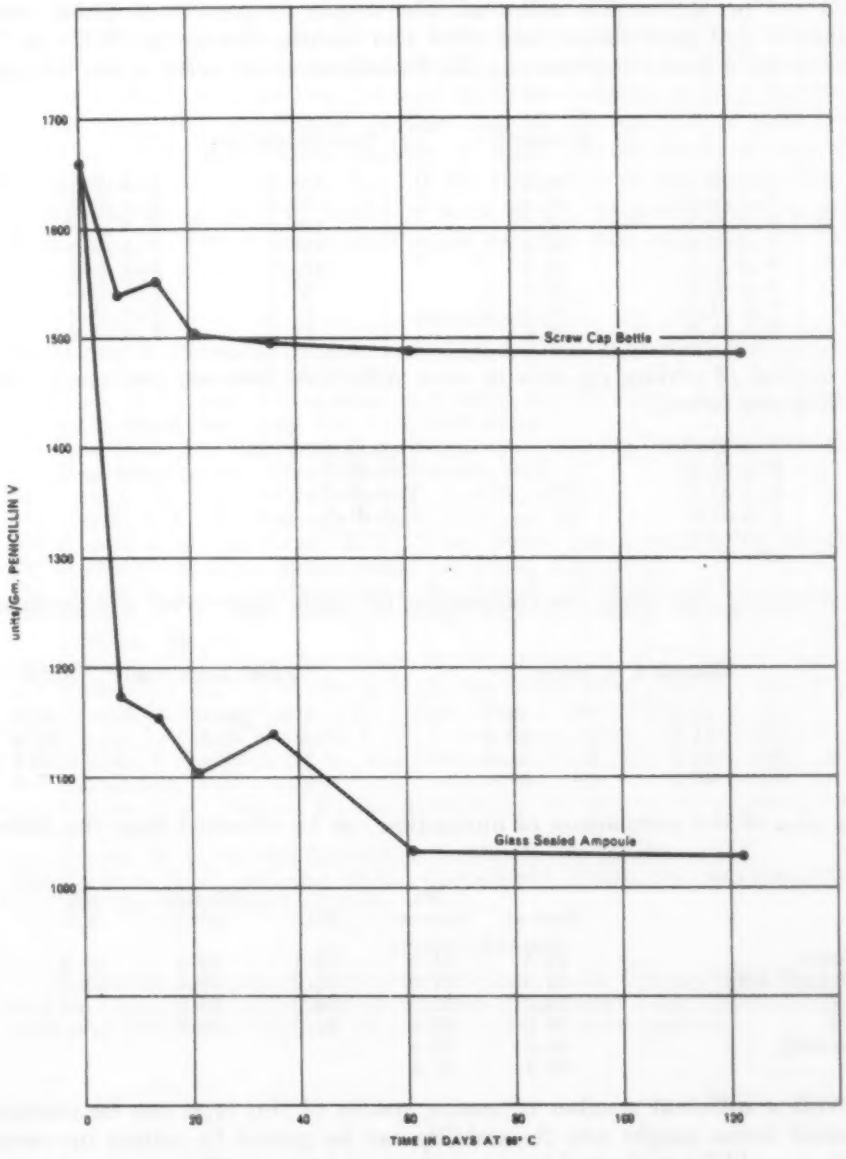

Fig. 7—DECOMPOSITION OF PENICILLIN V 1.14% MOISTURE

found in various books and articles on statistics (16, 17). One useful type of factorial experiment is outlined below:

P_1	Panthenol	P_2	Pantothenic Acid
A_1	pH 3.5	A_2	pH 6.4
B_1	Santoquin®	B_2	Butylated Hydroxyanisole
S_1	Sucrose	S_2	No Sucrose

Sixteen different combinations of these ingredients are available. The first column below is suitable for determining both individual affects and interaction between two ingredients. Only the eight variations of the first column were utilized because there was a good chance that at least one pair of ingredients would not be appreciably different. The results as percent of initial assay of Vitamin A and pantothenic acid after two months storage at 50°C. are listed between the columns representing the formulations, but refer to the left column only.

	Vitamin A	Pantothenic Acid	
$P_1A_1B_1S_1$	40.7	103.0	$P_1A_2B_2S_2$
$P_2A_2B_2S_2$	37.4	86.6	$P_2A_1B_2S_2$
$P_1A_1B_2S_2$	25.2	100.0	$P_2A_2B_1S_2$
$P_1A_2B_1S_2$	58.4	109.0	$P_2A_2B_2S_1$
$P_1A_2B_2S_1$	45.0	110.0	$P_2A_1B_1S_1$
$P_2A_2B_1S_1$	55.3	93.5	$P_1A_2B_1S_1$
$P_2A_1B_2S_1$	31.8	10.8	$P_1A_1B_2S_1$
$P_2A_1B_1S_2$	38.4	12.3	$P_1A_1B_1S_2$

The method of adding up data to show difference between two single ingredients is given below:

$P_1A_1B_1C_1$	$P_2A_2B_2C_2$
$P_1A_1B_2C_2$	$P_2A_2B_1C_1$
$P_1A_2B_1C_2$	$P_2A_1B_2C_1$
$P_1A_2B_2C_1$	$P_2A_1B_1C_2$
$4P_1$	$4P_2$

The results of this study on comparison of single ingredients are summarized below:

Vitamin A % Initial				Pantothenic Acid % Initial			
P_1	42.3	P_2	40.7	P_1	106.6	P_2	50.8
A_1	34.0	A_2	49.0	A_1	56.5	A_2	99.8
B_1	48.2	B_2	34.8	B_1	79.4	B_1	76.8
C_1	43.2	C_2	39.8	C_1	79.3	C_2	77.0

Some idea of the comparison of interaction can be obtained from the following table:

	Sucrose	No Sucrose	BHA	Santoquin®	pH 3.5	pH 6.4
Panthenol	42.8	41.8	35.1	49.5	32.9	51.7
Pantothenic Acid	43.5	37.9	34.6	46.8	35.1	46.3
pH 3.5	36.2	31.8	28.5	39.5		
pH 6.4	50.2	47.9	41.2	56.8		
Santoquin®	48.0	48.4				
BHA	38.4	31.3				

With a sufficient number of assays, results of this type can be statistically evaluated. Some insight into the stability can be gained by setting up comparisons that could be evaluated by an analysis of variance. Ten pieces of informa-

tion can be gained from an experiment of this type (eight experimental samples) compared with one piece of information from two experimental samples in a straight comparison. This type of approach can be helpful in determining the combination of ingredients which will offer the best stability in a particular type of preparation. Such a design may also be of use in evaluating pharmaceutical problems other than those concerned with stability.

It is not only desirable but essential to plan a stability evaluation in advance. Since the experimental preparation is usually the cheapest component of a stability study, it is advisable to have an oversupply in case someone drops a bottle or some other unforeseen circumstance occurs. Decide on what information you are seeking and then plan the experiment so that it should give this information. With accelerated studies it is best to have refrigerated or room temperature samples to be assayed over the proposed shelf life of the product. These samples will serve as a check and also can be used to either confirm or deny the assumption that the particular accelerated studies used in this case are a valid basis for a prediction. The approximate number of assays to be made during the study should be determined at this time. If the evaluation of the results does not give the information sought, it should at least give a suggestion for an experiment which will. In closing, we should again consider this question: Are the results worth the cost of the study?

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ISOTONICITY

FRANK M. GOYAN

Originally the term "isotonic" referred to uniform tension and, when applied to solutions, meant that the solutions produced the same tension or osmotic pressure. (1) Because natural membranes differ one from another, it seems reasonable to assume that the term isotonic refers to an ideal semi-permeable membrane rather than some unspecified natural membrane. (2) However, recent usage seems to reserve the term "iso-osmotic" for ideal membranes. (3, 4, 5) The need for a different treatment for the same solution for each different natural membrane renders the word isotonic ambiguous for general purposes and suggests the need for a slightly different nomenclature when referring to the usual calculations based on various colligative properties.

Some years ago the author suggested the use of the term "isotonicity value" or "tonicity value" to describe an osmotic property of a solution in much the same way that the term "pH value" describes an acidity property. (6) The idea of a "tonicity" scale or "isotonicity scale" was developed in terms of per cent of sodium chloride. The advantages of speaking of an isotonicity value rather than declaring a solution to be isotonic with some standard substance such as blood serum are practical as well as logical. From the practical point of view it is easier to work with a concept that can be visualized in terms of a pointer moving along a scale. The logical advantage of a defined isotonicity value is that it can (by definition) be divorced from the implication of biological infallibility without creating the impression that it is a radical departure from the conventional isotonic calculations that have occupied the attention of pharmacists for nearly a century (7, 8, 9).

Husa and his co-workers have made a tremendous contribution in showing that solutions of many substances having an isotonicity value of 0.9% NaCl lack the ability to protect red blood cells of man and certain animals from hemolysis (10–20). Boric acid is one of these substances (10), yet is well known that boric acid has been used in ophthalmology without complaint for many years (21). It is obvious that the membranes of the eye which are exposed to external treatment are not the same as the membrane surrounding red blood cells. This fact undoubtedly accounts for the acceptability of collyria made up to an isotonicity value of 0.9% NaCl by the addition of boric acid, and suggests the need for further refinement of the isotonicity notation by including an abbreviation which specifies the membrane involved in the determination. However, the toxicity of boric acid when taken internally or applied to damaged skin indicates that more than the permeability of membranes may be involved (22). Practically, the biological problems are much too complex to lend themselves to simple scalar notation at this time. Hammarlund and Pedersen-Bjergaard have shown that isoosmotic solutions that hemolyze red blood cells often show 100% hemolytic action (5). In other words, they show no protective action whatsoever. If it were desirable to develop a notation to include the biological differences, such solutions might

be assigned isotonicity values of 0.9% NaCl (f.p.) and X% NaCl (hem.) The meaning of this notation is obvious: the abbreviation (f.p.) indicates that the value of 0.9% NaCl was assigned on the basis of freezing point measurements and the abbreviation (hem.) indicates that the undetermined value of X was assigned on the basis of hemolytic studies. However, it is not the purpose of this paper to recommend such notation, but rather to call attention to the suggestion of Setnikar that substances can be listed which are better dissolved for injection in 0.9% NaCl without attempting calculation of isotonicity values (3, 4). There is no evidence that the same list would apply to ophthalmic soluions.

Practical Calculations

When a pharmacist is asked to render a solution isotonic, he is seldom given much additional information. However, he always knows or can find out the intended use of the solution he is preparing. If he is making a solution for a laboratory where the intended use is to dilute blood, he obviously must consider hemolysis of red blood cells. Furthermore, he would have to discover what species of animal was under investigation. By the same token, he would investigate with great care the hemolytic properties of any solution intended for injection into the blood stream of man in significant volume. However, these same considerations might not apply for solutions intended for use on mucosa or for ophthalmic use.

In almost all cases where the pharmacist is asked to make a solution isotonic extemporaneously, it is assumed that he will adjust the solution to an isotonicity value of 0.9% NaCl. For ophthalmic use, it has been determined that solutions that fall in the range from 0.7% NaCl to 1.5% NaCl will cause no difficulty (23). Available reference material can be consulted to find some one common denominator by which the osmatic properties of each ingredient can be evaluated.

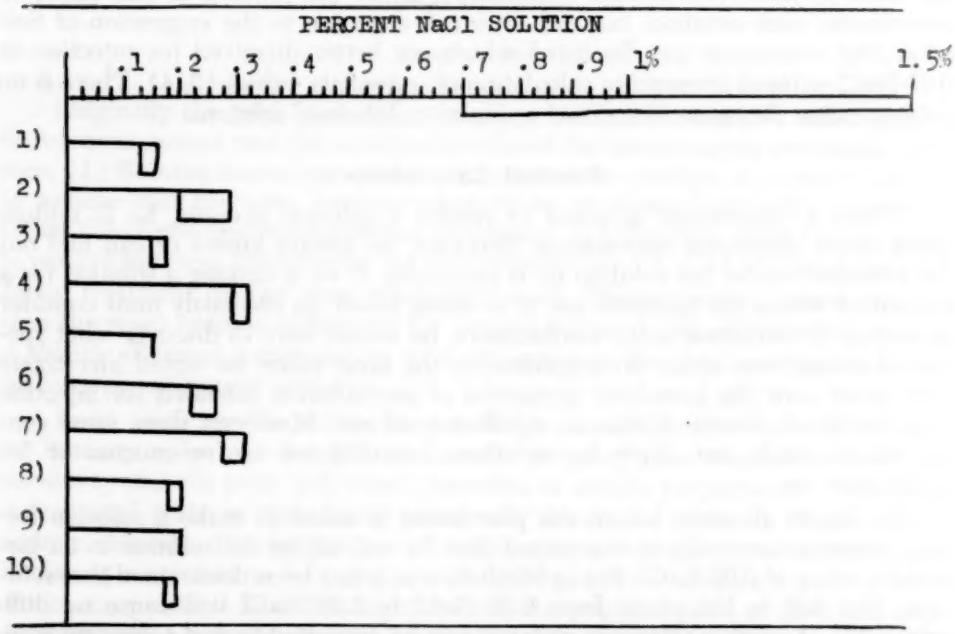
Freezing Point Method

Tables of the lowering of the freezing point produced by definite concentrations of various substances in water have been constructed. The freezing point of blood serum may be taken as −0.53°C. corresponding to a 0.9 solution of NaCl or to −0.56 corresponding to a 0.95% solution. The latter is often used but is gradually falling into disuse because it seems more desirable to make the freezing point and the NaCl per cent agree (24). In any event, once the decision is made to make a solution to have a chosen freezing point, it is a simple matter to add together all of the freezing-point contributions from the different components of the solution. Subtracting this sum from the desired freezing point gives a number that may be treated by proportion or ratio to determine how much of some additional substance is required. Excellent samples of this method are given in standard works (8).

Sodium Chloride Equivalent Method

The Sodium Chloride Equivalent method differs from the freezing point method only in substituting for freezing point lowering the weight of sodium chloride that has the same osmotic effect as the various constituents. The sum of all of these values is subtracted from the weight of sodium chloride required. This method is also given with examples in standard reference (9).

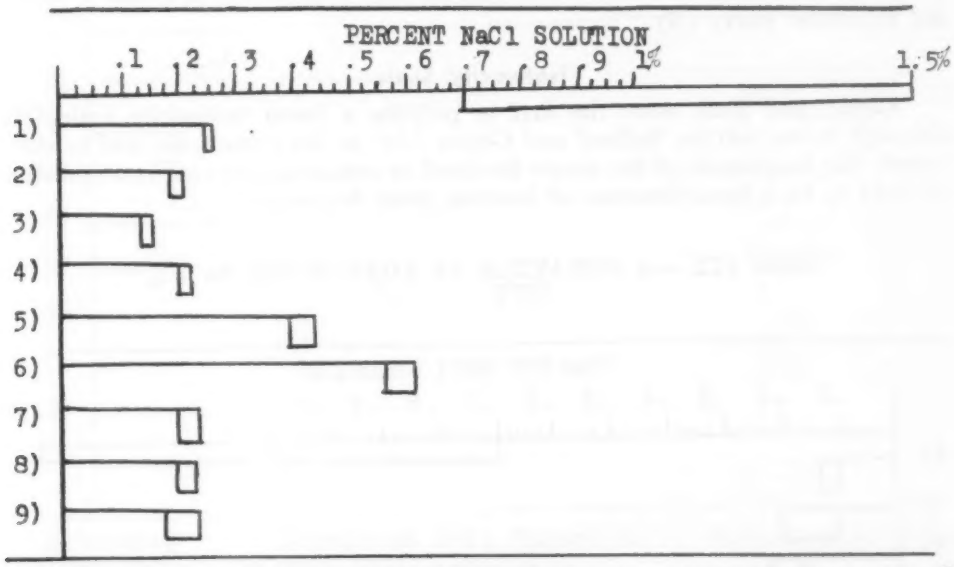
TABLE I.--A COMPARISON OF CHLORIDES OF THE NaCl TYPE



Substance	Calculated NaCl Equivalent E=58/M	Experimental Value*
1) Dibucaine HCl	0.15	0.13
2) Diphenhydramine HCl	0.20	0.28
3) Ethylhydrocupreine HCl	0.15	0.17
4) Methacholine chloride	0.30	0.28
5) Morphine HCl (3 H_2O)	0.15	0.15
6) Naphazoline HCl	0.23	0.27
7) Phenylephrine HCl	0.28	0.32
8) Piperocaine HCl	0.19	0.21
9) Procaine HCl	0.21	0.21
10) Tetracaine HCl	0.19	0.18

*E=sodium chloride equivalent at a 1% concentration. Values obtained from the work of Hammerlund and Pederson-Bjergaard 1958.

TABLE II.--A COMPARISON OF OTHER SALTS OF THE NaCl TYPE



Substance	Calculated NaCl Equivalent E= 58/M	Experimental Value*
1) Hydroxyamphetamine HBr	0.25	0.26
2) Neostigmine bromide	0.19	0.22
3) Physostigmine salicylate	0.14	0.16
4) Pilocarpine nitrate	0.21	0.23
5) Sodium biphosphate (H_2O)	0.42	0.40
6) Sodium biphosphite	0.56	0.61
7) Sulfadiazine sodium	0.21	0.24
8) Sulfamerazine sodium	0.20	0.23
9) Sulfathiazole sodium	0.19	0.22

*E=sodium chloride equivalent at a 1% concentration. Values obtained from the work of Hammerlund and Pederson-Bjergaard 1958.

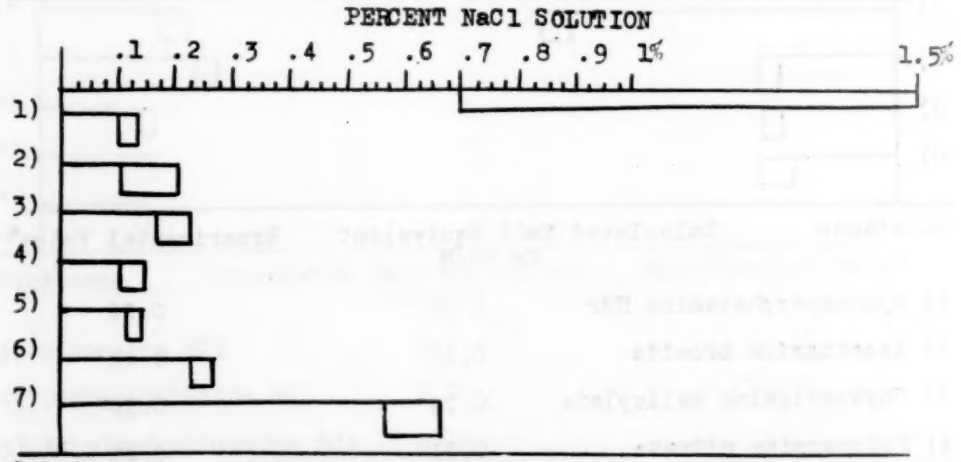
Diluting Solutions Method

White and Vincent (25) and Greco (26) proposed calculating the volume of water required to bring each individual constituent to some predetermined isotonic concentration. Greco published a table containing many of these values. After the required amount of water is added, the solution is brought up to volume with a suitable isotonic vehicle. This method is described in detail in standard reference works (9).

Isotonicity Scale

Goyan and Reck were the first to propose a linear isotonicity scale (6), although it was left for Ballard and Goyan (24) to draw the scale and to show exactly the magnitude of the errors involved in assuming per cent concentration of NaCl to be a linear function of freezing point depression.

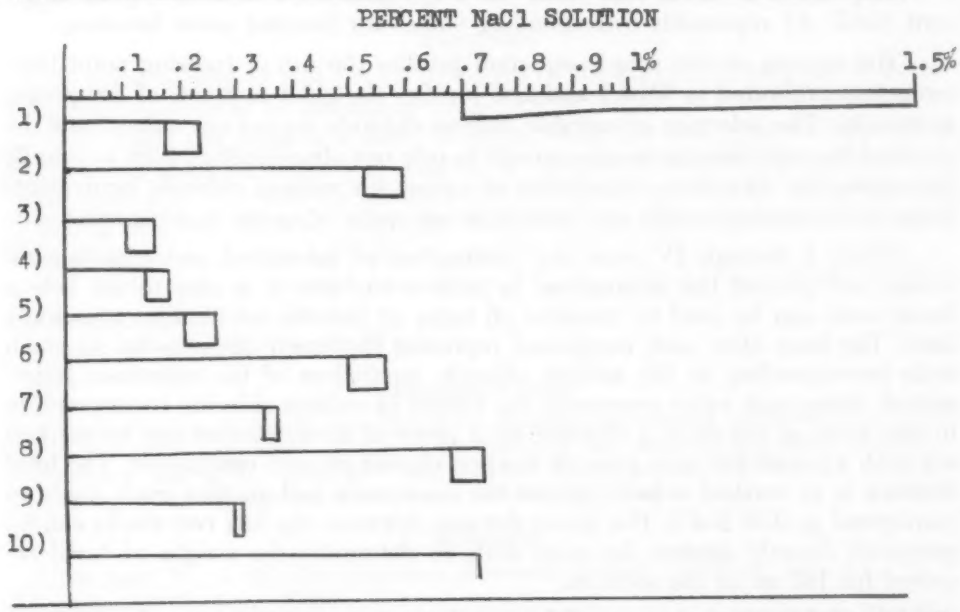
TABLE III.--A COMPARISON OF SALTS OF THE Na_2SO_4 TYPE



Substance	Calculated NaCl Equivalent E= 73/M	Experimental Value*
1) Atropine sulfate	0.10	0.13
2) Butacaine sulfate	0.10	0.20
3) Ephedrine sulfate	0.17	0.23
4) Morphine sulfate	0.10	0.14
5) Physostigmine sulfate	0.11	0.13
6) Sodium sulfate (10 H_2O)	0.23	0.26
7) Sodium sulfite	0.57	0.65

*E=sodium chloride equivalent at a 1% concentration. Values obtained from the work of Hammerlund and Pedersen-Bjergaard 1958.

TABLE IV.--A COMPARISON OF SEVERAL DIFFERENT SUBSTANCES



Substance	Calculated NaCl Equivalent	Experimental Value*
(Dextrose-boric acid type)	E=32/M	
1) Chlorbutanol	0.18	0.24
2) Urea	0.53	0.59
(Zinc Sulfate type)	E=34/M	
3) Zinc sulfate (7 H_2O)	0.11	0.15
4) Cupric sulfate (5 H_2O)	0.14	0.18
5) Cupric sulfate (anhyd.)	0.21	0.27
(Calcium Chloride type)	E=82/M	
6) Calcium chloride ($2H_2O$)	0.56	0.51
7) Calcium chloride ($6H_2O$)	0.37	0.35
8) Calcium chloride (anhyd.)	0.74	0.68
(Sodium citrate type)	E=88/M	
9) Sodium citrate (2 H_2O)	0.30	0.31
(Aluminum chloride type)	E=102/M	
10) Aluminum chloride	0.72	--**

*E=sodium chloride equivalent at 1% concentration. Values obtained from the work of Hammerlund and Pederson-Bjergaard 1958.

**No experimental value reported.

Within the range of 0 to 2 per cent NaCl the equation $I_p = (0.90/0.53)\Delta T$, fits the data of Scatchard and Prentiss with a maximum error of 0.007% NaCl at a scale position of about 0.5% NaCl (27). I_p represents isotonicity values in per cent NaCl. ΔT represents corresponding values for freezing point lowering.

The success of this simple equation justifies the use of freezing point thermometers calibrated in %NaCl and also justifies the older methods of computing isotonicity. The selection of suitable sodium chloride equivalent values must be checked by experimental measurements to rule out abnormalities such as micelle formation, etc. However, calculation of values for sodium chloride equivalents based on molecular weight and ionic type are quite adequate in most cases.

Tables I through IV show the comparison of calculated and experimental values and present the information in such a way that it is easy to see how a linear scale can be used to visualize all types of isotonic calculations commonly used. The lines after each compound represent the linear distance on the main scale corresponding to the sodium chloride equivalent of the substance represented. Since each value represents the weight of sodium chloride corresponding to one gram of the drug, a distance on a piece of scratch paper can be marked out with a pencil for each gram of fraction thereof of each constituent. The total distance is so marked is held against the main scale and another mark made to correspond to 0.9% NaCl. The linear distance between the last two marks can be measured directly against the main scale to determine the weight of NaCl required for 190 ml of the solution.

It will be noted that the difference between experimental and calculated value is indicated by a block at the end of each line. For many preparations, these blocks do not indicate significant error. It is easy to see which end of the block represents the experimental value by glancing at the table below each linear representation.

Although these diagrams could be extended to include the complete table of sodium chloride equivalent values, it is doubtful if such a representation would be of great practical value because it is so easy to compute the sum of the NaCl equivalent contributions and subtract from 0.9 without graphical aid (28). However, as a teaching aid in showing what operations are involved and the approximate accuracy required, the graphical method is of considerable value. Of course the development of a linear scale of isotonicity has many other potential uses both in instrumentation and in teaching.

Those wishing to use diluting solutions will observe that the linear summation read on the main NaCl scale may be multiplied by (100/0.9) to obtain the volume of water required to render the constituents isotonic before adding diluting vehicle. This follows from the simple fact that 100 ml. contains 0.9 Gm of NaCl. The arithmetic can be done mentally by shifting the decimal two places and adding 11% of the resulting reading.

When working in apothecary units, it is not necessary to make elaborate conversions. NaCl equivalents can be read in any consistent weight units. All that is necessary is to draw an extension of the main NaCl scale and mark the value, which is the number of grains of NaCl per fluid once needed to produce a solution having an isotonicity value of 0.9% NaCl. Obviously such drawing is important only to illustrate the point and need not be carried out except as a teaching aid.

It will be noted that the range regarded as safe for ophthalmic work is marked with a bar on the main scale to aid in visualizing the magnitude of allowable approximation for some work.

Examples

1. What weight of NaCl must be added to 100 ml of a 2% solution of Tetracaine HCl to develop an isotonicity value of 0.9% NaCl?

Ans. Hold the edge of a sheet of paper along the line opposite item 10 of Table I and mark off twice the distance of this line. Transfer the paper to the upper scale and note that the distance marked comes to .38. This is the I_p value of the 2% solution. Subtract this value from 0.90 (graphically or mentally) and obtain 0.52 as the weight of NaCl required.

2. How much water must be added to 2 Grams of Tetracaine HCl to develop an I_p value of 0.9% NaCl?

Ans. $0.38 \times (100/0.9) = 42$ ml.

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BUFFERS

JOHN L. LACH

The recognition of the importance of "buffers" in physiological processes and all branches of chemistry has resulted in a wealth of information concerning their properties, preparation, and uses. Pharmaceutically speaking, buffers have been employed in areas of solubilization, stabilization, product development, and manufacture and control of medicaments to name but a few. The properties of such solutions were first discussed by Henderson (1) and by Washburn (2) in 1908, and some fifty years has elapsed since Sorenson (3), in his report on buffers, introduced the "pH" concept for expressing hydrogen ion concentration.

Since the practice of pharmacy today may require the use of buffer solutions and will do so even more in the future, it is my feeling that this area be presented thoroughly in our undergraduate curriculum. It is certainly possible for the student to understand the many problems of buffer systems and hydrogen ion concentration without having a highly technical background, particularly in the subject of mathematics. I should like, therefore, to present an undergraduate approach to this problem of buffer solutions. It is also hoped that this approach could easily be expanded for graduate purposes.

Buffers have been defined as "substances which by their presence in solutions increase the amount of acid or alkali that must be added to cause unit change in pH." (4) They may also be defined as those substances which prevent sudden or great changes in hydrogen ion concentration when strong acids or bases are added to a system. For example, if one adds a small amount of acid or base to water or a solution of sodium chloride, the hydrogen ion concentration or pH is considerably altered. However, the addition of a small amount of acid or base to a solution containing equal quantities of acetic acid and its conjugate base, sodium acetate, results in a very small change in the pH of the solution. This small change, in the latter case, can be explained on the basis of the removal of hydrogen ion by the acetate ion (conjugate base) according to the following reaction:

$$Ac^- + H_3O^+ \rightleftharpoons HAc + H_2O$$

If a strong base, such as sodium hydroxide, is added to the solution of acetic acid and sodium acetate, again no appreciable change in pH is observed due to the neutralization of the hydroxyl ions by the acetic acid as shown in the following reaction:

$$HAc + OH^- \rightleftharpoons H_2O + Ac^-$$

Buffer action, then, is a consequence of the equilibria between water, the weak acids (HA), bases (B), and ampholytes (Z) and the ions into which these several species are partially converted in aqueous solution.

$$HA + H_2O \rightleftharpoons A^- + H_3O^+$$

$$B + H_2O \rightleftharpoons BH^+ + OH^-$$

$$Z^{\pm} + H_3O^+ \rightleftharpoons Z^+ + H_2O$$
$$Z^{\pm} + OH^- \rightleftharpoons Z^- + H_2O$$

The preparation of buffer solutions then involves the use of

a. a weak acid and its salt
b. a weak base and its salt
c. acid salts

The estimation or calculation of hydrogen ion concentration or pH in such mixtures often causes considerable difficulty to the beginning student. It should be pointed out, however, that certain assumptions and simplifications are possible, even in relatively complex systems, in order that a reasonable estimate of the hydrogen ion concentration be obtained. This can be clearly illustrated in the dissociation of a weak acid, such as acetic acid, in water. The effect of changes in concentration (molarity) and activity of the participating species is expressed quantitatively by the mass law. Thus for the monobasic acid, one can write the dissociation constant as

$$K_a = \frac{(A_{H_3O^+})\,(A_{Ac^-})}{(A_{HAc})} = \frac{(\gamma_{H_3O^+}C_{H_3O^+}) \times (\gamma_{Ac^-}C_{Ac^-})}{\gamma_{HAc}C_{HAc}}$$

where A = activity of the ionic species = activity coefficient × molarity. This equation, although thermodynamically correct, may add little to the beginning student's overall understanding of chemical equilibria. Since one usually deals with dilute solutions, certain assumptions and simplifications can be introduced. In dilute solutions, the activity coefficient of an ion may be set equal to unity, that is, activity, of the acid then is equal to its concentration and the dissociation constant may be written in terms of the concentration of the species as follows:

$$HAc + H_2O \rightleftharpoons H_3O^+ + Ac^-$$
$$Ka = \frac{[H_3O^+]\,[Ac^-]}{[HAc]}$$
$$[H_3O^+] = Ka\,\frac{[HAc]}{[Ac^-]}$$

From these relationships, it becomes apparent that when a salt, such as sodium acetate is added to a solution of acetic acid, ionization of the acid is repressed since the concentration of acetate ions is increased. In order that Ka remain constant, hydrogen ion must be removed from the solution and appears as the undissociated acid HAc.

If we assume that the acid undergoes only slight ionization, then HAc may be considered as representing the total acid concentration in solution. If we also assume that the total acetate ion concentration has resulted from the dissociation of the salt, then our expression for the dissociation constant may be written as

$$[H_3O^+] = Ka\,\frac{[Acid]}{[Salt]}$$

In logarithmic form the equation becomes

$$pH = pK_a + \log\frac{[Salt]}{[Acid]}$$

This equation is commonly known as the buffer equation or as the Henderson-Hasselbach equation.

A similar treatment for solutions of weak bases and their salts leads to the following equation:

$$pH = pK_w - pK_b + \log \frac{[Base]}{[Salt]}$$

In dealing with buffers prepared from salts of polyvalent acids, we can, with similar assumptions and simplifications, arrive at the following equation:

$$pH = pK_n + \log \frac{[Salt]}{[Acid]}$$

n = stage of dissociation

For a solution consisting of NaH_2PO_4 and Na_2HPO_4, the former acts as the acid and the latter as the salt. Here n is equal to 2 since the second stage of ionization is involved.

The mechanism involved in buffer action can be readily described by illustration of a typical titration curve of a weak acid, such as acetic acid, and a strong base (NaOH). Symbol B, on this curve, is the half neutralization point in the titration, and at this one-half point, one-half of the acid has been converted to a salt making the salt/acid ratio equal to 1. It is also clearly seen from this titration curve that from point A to C, addition of base to the acid solution results in a shift of the salt/acid ratio without any appreciable change in pH. From this titration curve and from our buffer equation

$$pH = pKa + \log \frac{[Salt]}{[Acid]}$$

it is clearly seen that the best buffers are prepared when equal amounts of salt and acid are used, or when the $\log \frac{salt}{acid}$ ratio is equal to 1. It may also be pointed out at this time that this ratio of salt to acid should not exceed 100 or fall below $\frac{1}{100}$, for then the buffer action is lost. Generally speaking, buffer mixtures in which the pH lies between $pK_a - 1.7$ and $pK_a + 1.7$ may be satisfactorily prepared from a weak acid and its salt.

Equations of the type presented are best understood by the beginning student when applied to pharmaceutical systems. Therefore, it is important that sufficient time be spent in this area of problem application.

It soon becomes evident to the student that not all mixtures of weak acids and their salts have the same ability to maintain a constant hydrogen ion concentration that certain pharmaceuticals, in a particular formulation, may cause a shift in pH beyond the effective buffer region of the solution. This more quantitative concept of buffer capacity or buffer efficiency can be introduced. Van Slyke, in his original work on the mathematical aspects of buffers, introduced this important concept and defined "buffer capacity" or "buffer efficiency" as the ratio of the increment of strong acid or base added to the small change in pH brought about by this addition and expressed in approximate terms as

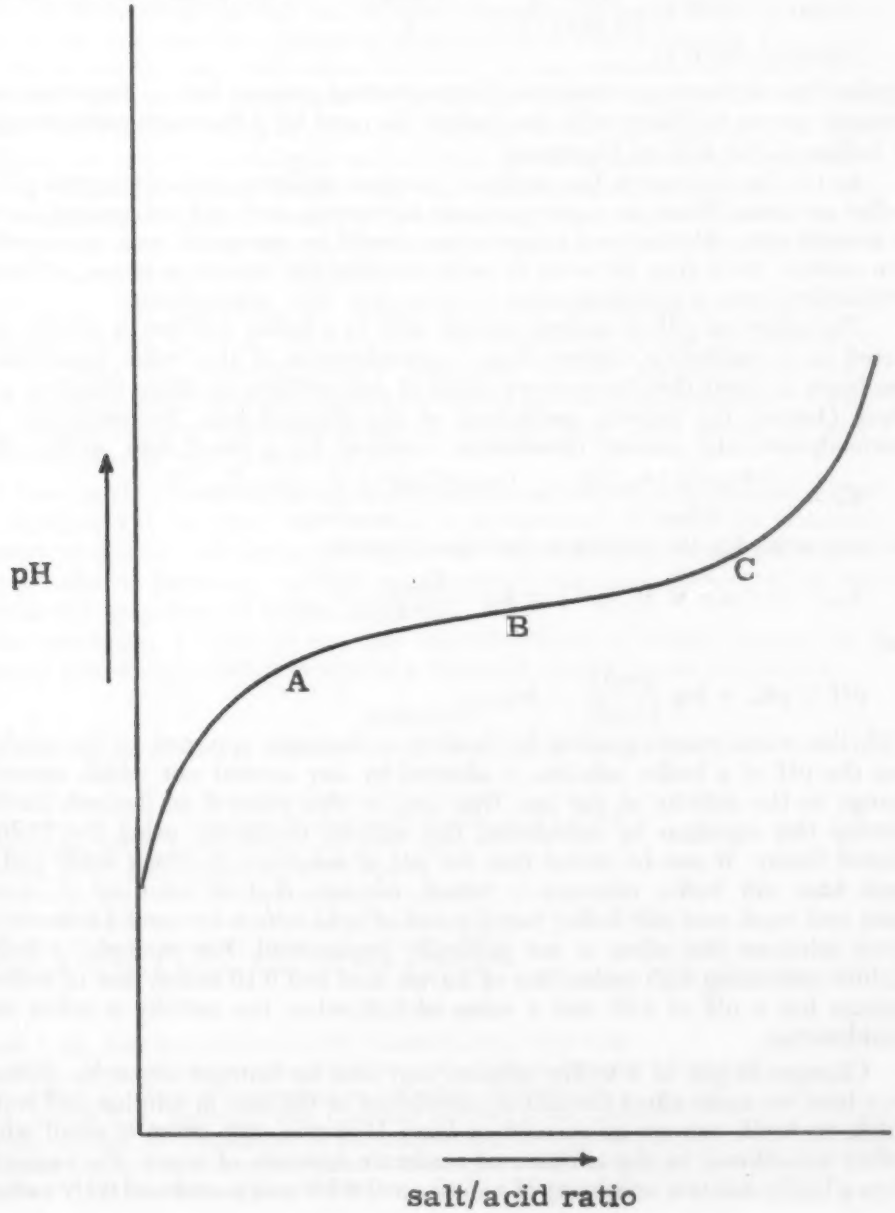
$$\beta = \frac{\Delta B}{\Delta pH}$$

where ΔB is the small increment in gm. equiv. /L of strong acid or base added to the buffer solution to cause a change in ΔpH of pH units (4). A buffer solution, then, has a capacity of 1. when one gm. equiv. of acid or base results in a pH

change of one unit. Here no sign is specified; this change is positive and the buffer capacity is also positive. Since this approximate equation for buffer capacity gives only the average buffer capacity over the increment of base or acid added and is satisfactory for formulation purposes, a more exact equation which describes this capacity at any hydrogen ion concentration can be developed and is

$$\beta = 2.303\,C\,\frac{[Ka\,(H_3O^+)]}{[(Ka + (H_3O^+)]^2}$$

where C is the total buffer concentration, that is, the sum of the molar concentrations of acid and the salt.



Such an equation, then, permits the student to calculate the Gm. equiv. /L of acid or base that may be added to a buffer without an appreciable change in pH. As already pointed out from our titration curve, the best buffer capacity occurs when the ratio of $\log \frac{[salt]}{[acid]}$ is equal to 1 or when pH = pKa or in equivalent terms when the hydrogen ion concentration is equal to Ka. Substitution of the hydrogen ion concentration in the general equation for buffer capacity permits the calculation of the maximum buffer capacity of the solution as follows:

$$\beta \text{ max} = 2.303 \text{ C} \frac{[H_3O^+]^2}{[2(H_3O^+)]^2} = \frac{2.303C}{4}$$

$$\beta \text{ max} = 0.576 \text{ C}$$

Application of these equations to pharmaceutical systems here is important and certainly serves to illustrate to the student the need for a thorough understanding of buffers in the field of pharmacy.

So far this discussion has made no mention of factors influencing the pH of buffer solutions. From an undergraduate viewpoint, such pH influencing factors as neutral salts, dilution, and temperature should be presented even in a qualitative manner since they do serve to point out that the equations in use, although satisfactory from a practical point of view, are only approximate.

The effect on pH of adding neutral salts to a buffer solution is readily predicted in a qualitative manner from a consideration of the buffer equilibria if one bears in mind that the primary effect of salt addition in dilute solutions is to affect (lower) the activity coefficients of the charged ions. Reconsidering our thermodynamically correct dissociation constant for a weak acid, acetic acid,

$$K_a = \frac{(A_{H_3O^+})(A_{Ac^-})}{(A_{HAc})} = \frac{(\gamma_{H_3O^+} C_{H_3O^+}) \times (\gamma_{Ac^-} C_{Ac^-})}{\gamma_{HAc} C_{HAc}}$$

one can write for the hydrogen ion concentration

$$A_{H_3O^+} = (\gamma_{H_3O} \times (C_{H_3O^+}) = Ka \frac{C_{HAc^-}}{\gamma_{Ac^-} C_{Ac^-}}$$

and

$$pH = pK_a + \log \frac{[Salt]}{[Acid]} + \log \gamma_{Ac^-}$$

With this more exact equation for buffers, it becomes apparent to the student that the pH of a buffer solution is affected by any neutral salt which causes a change in the activity of the ion. One can, at this point if so desired, further develop this equation by calculating this activity coefficient using the Debye-Huckel theory. It can be stated that the pH of solutions of strong acids and of weak base salt buffer mixtures is raised, whereas that of solutions of strong bases and weak acid salt buffer mixture and of acid salts is lowered. However, in dilute solutions this effect is not generally pronounced. For example, a buffer mixture containing 0.05 moles/liter of formic acid and 0.10 moles/liter of sodium formate has a pH of 4.05 and a value of 3.93 when the activity is taken into consideration.

Changes in pH of a buffer solution may also be brought about by dilution since here we again affect the activity coefficient of the ions in solution and water which, in itself, can act as an acid or base. However, this effect is small when buffers are diluted by the addition of moderate amounts of water. For example, when a buffer solution consisting of a mixture of 0.1N acetic acid and 0.1N sodium

acetate is diluted forty fold the pH change is from 4.61 to 4.70. This dilution effect may be expressed in a quantitative manner by defining a quantity $\Delta pH_{1/2}$ (the dilution value) as

$$\Delta\, pH_{1/2} = (pH_{c_{1/2}}) - (pH)_{c_1}$$

where Ci is the original pH, Ci/2 is the pH at one-half the original strength and $\Delta\, pH_{1/2}$ is the pH change at this dilution (5).

Since the dissociation constants of most acids used in buffer mixtures vary slightly with changes in temperature, one would expect that changes in pH of acid buffers with temperature would be relatively small (6). Kolthoff and Tekelenburg, in their study of this temperature dependency for a large number of buffers, point out that this change is slight for most buffer systems (7). However, this is not the case with basic buffers since the ionization of water (Kw) is extremely sensitive to temperature. The ion product of water at 100° is about one hundred times its value at room temperature, or the pKw varies by a factor of 2. Since Kw appears in the general equations for basic buffers, the temperature effect on pH in such basic buffers may be significant. For example, in a basic buffer consisting of equal amounts of ammonia and ammonium chloride, the pH at 25° is 9.24 whereas at 50° the pH is 8.54. The use of such basic buffers in pharmacy is certainly not encouraged.

Although this discussion of buffers has been developed in terms of the Arrhenius concept, I should like to point out that the subject of acid-base equilibria involving the Bronsted theory may offer further simplifications and a clearer understanding of these buffer solutions to the student. A number of interesting papers dealing with this Bronsted concept have been published and I should like to refer you to them (8, 9).

I have made no attempt here to discuss the subject of buffers from a graduate standpoint. I am sure that in such a presentation it would be absolutely necessary to discuss and derive the equations from a thermodynamic standpoint. It would also be necessary to treat quantitatively the many factors which may influence the properties of buffer solutions

In conclusion, I want to say that the importance of buffer systems in all phases of pharmacy certainly warrants a thorough review in our curriculum.

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HYDROGEN BONDED COMPLEXES IN NONPOLAR SOLUTIONS—INFLUENCE OF STRUCTURE AND SOLVENT ON FORMATION TENDENCY AND STOICHIOMETRY

TAKERU HIGUCHI

Relatively little past effort has been directed toward understanding of ternary systems involving formation of hydrogen bonds among solute molecules dispersed in nonpolar solvents. The present communication is concerned with some quantitative data obtained from solubility experiments on the stoichiometry of these interactions and the relative proton accepting tendencies of some common oxygenated functional groups. The results suggest that the interaction behaviors are largely characteristic of the functional groupings present and essentially constant for a homologous series.

Basis of the Solubility Method

Since the conclusions arising from these studies are based on solubility analysis, it may be pertinent to point out some of the characteristics of this technique. If an excess of a crystalline substance A is placed in an essentially nonpolar solvent (carbon tetrachloride, cyclohexane, etc.) which does not possess stereospecific interaction sites, we could write

$$A_s \rightleftharpoons [A_1] + [A_2] + [A_3] + \ldots . \qquad (1)$$

where the subscript refers to the several discrete states of aggregation of the solute in solution. The thermodynamic activity of each is, of course, equal to that of the solid. And

$$\sum_{n=1}^{\infty} n[A_n] = \text{observed molar solubility of A in S} = A_s.$$

If into this system we introduce a second solute component (B) in a subsaturation amount capable of undergoing specific interaction with the first and if we assume both components to be present still in a relatively low concentration, we can write the solute species as

$$[A] + [A_2] + [A_3] + \ldots [A_n] + [B] + [B_2] + \ldots [B_m] + [AB] + [AB_2] + \ldots [AB_m] + [A_2B] + [A_2B_2] + \ldots [A_2B_m] + \ldots [A_nB_m]$$

Or the apparent solubility of A,

$$A_t = A_s + ([AB] + [AB_2] + \ldots) + 2([A_2B] + [A_2B_2] + \ldots) + \ldots . \; n([A_nB] + [A_nB_2] + \ldots) \qquad (2)$$

The higher terms are not normally significant at low dilutions for most systems. Generally for practical purposes the following embraces all of the important terms.

$$A_t = A_s + (AB) + (AB_2) + (A_2B)$$

For systems saturated with A the above would lead to a quadratic function with respect to the concentration of monomeric B, (B), where the constant term corresponds to A_s, the linear term to the total concentration of all species containing one molecule of B, and the quadratic term the total concentration of all terms containing two molecules of B. It is evident then that for these systems a

plot of A_t against (B) would yield a great deal of information on the complexing tendencies of A with B. One of the difficulties inherent in this approach, however, is in obtaining an accurate measure of (B), the concentration of the free monomeric form of the added material.

For very dilute solutions of B and where the binding tendencies toward A are relatively weak we can safely assume for many substances that the added B will exist in solution as the free monomer with a small stoichiometric correction for that part which forms complex species with A. This would be particularly true for case where B has a single binding site such as a simple ether, ketone, ester or an aldehyde molecule. For systems which tend to associate very strongly, however, the problem of estimating monomer concentration becomes a good deal more difficult. The total amount of B added ends up as complexes with A and/or in the form of dimeric and higher associated species of B. Reliable estimation of monomeric B, in this situation, becomes rather difficult. For these reasons studies reported below have been largely limited to relatively low total concentration of B.

Equilibrium concentration of each solute species present in these mixtures follows the law of chemical potential. For the complete species we can therefore write

$$\begin{aligned} K'_{AB} f_A [A] f_B [B] &= f_{AB}[AB] \\ K'_{A_2B} f_{A_2} [A_2] f_B [B] &= f[A_2B] \\ &\text{etc.} \end{aligned} \qquad (3)$$

Since the activity of all the species of A is the same and equal to that of the solid we can write, for example,

$$K_{AB}^{\pm} = \frac{f_{AB}\ [AB]}{f_B\ \ [B]} \text{ where } K_{AB}^{+} = K'_{AB} \text{ (Activity of solid A).} \qquad (4)$$

Equation (4) is a general equation valid for all systems. For different solvent

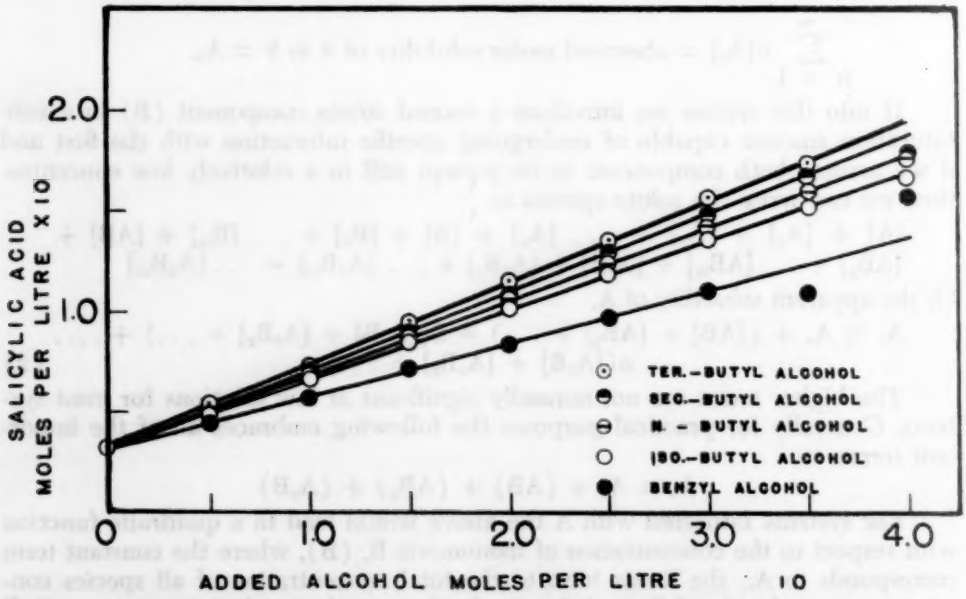

Figure 1.—Phase diagram showing the hydrogen bond formation between salicylic acid and various alcohols.

systems it is evident that the ratio of AB to B will be the same if the activity coefficients f_{AB} and f_B are similarly affected. It is apparent that similar relationships hold for other complex species.

Experimental Observations and Discussion

The general influence of a proton accepter on the solubility of a proton donor is shown in Figure *1*. The equilibrium solubility of salicylic acid in carbon tetrachloride as affected by different alcohols has been plotted as functions of their concentrations. For this particular system apparently the complex species of any importance contain only one molecule of the proton accepter (alcohol) since the solubility of the acid increases linearly with the alcohol concentration.

$$A + B \underset{\leftarrow}{\overset{K_{AB}}{\rightleftharpoons}} AB$$

and

$[AB] = K_{AB}'' [A] [B]$ where K_{AB}'' is the equilibrium constant based on concentration in given solvent. It is more convenient to include [A] in the constant and write

$$K_{AB} = \frac{[AB]}{[B]} = \frac{[AB]}{[B_o] - AB} \tag{5}$$

for measurements made in equilibrium with solid A where $[B_o]$ is the added B and [B] is the free B.

Equation (5) can be transformed into

$$\frac{K_{AB}}{K_{AB} + 1} = \frac{[AB]}{[B_o]} = \text{slope} \tag{6}$$

The slope values can be readily read from plots such as shown in Fig. *1* and K_{AB} constants calculated for different systems.

This has been done for various alcohols and phenol and the results are shown in Table I. It is evident that the formation constants for all the normal, straight chain alcohols are essentially the same. Qualitatively, the others behave essentially as would be expected on the basis of their proton accepting tendency. One would suspect, however, that these alcohols operate bifunctionally to some extent since they also possess bondable hydrogen.

TABLE I—COMPLEX FORMATION CONSTANTS BETWEEN SALICYLIC ACID AT SATURATION AND VARIOUS ALCOHOLS AND PHENOL IN CARBON TETRACHLORIDE AT 30°

Alcohols	Slopes	$K_{AB} = \frac{\text{Complex}}{\text{Free Alcohol}}$
Ethanol	0.369	58.5×10^{-2}
Butanol	0.365	57.5
Octanol	0.367	58.0
Dodecanol	0.359	56.0
Isobutyl	0.342	51.9
Sec. butyl	0.385	62.6
Ter-butyl	0.405	68.0
Cyclohexyl	0.403	67.5
Benzyl	0.256	34.4
Phenol	0.090	9.9

In Table II are listed some observed formation constants (K_{AB}) for various, oxygen containing molecules. Except for the triphosphate the alkyl amides show by far the strongest complexing tendency. With these stronger proton acceptors the slope values are very close to one and the exact constants cannot be deter-

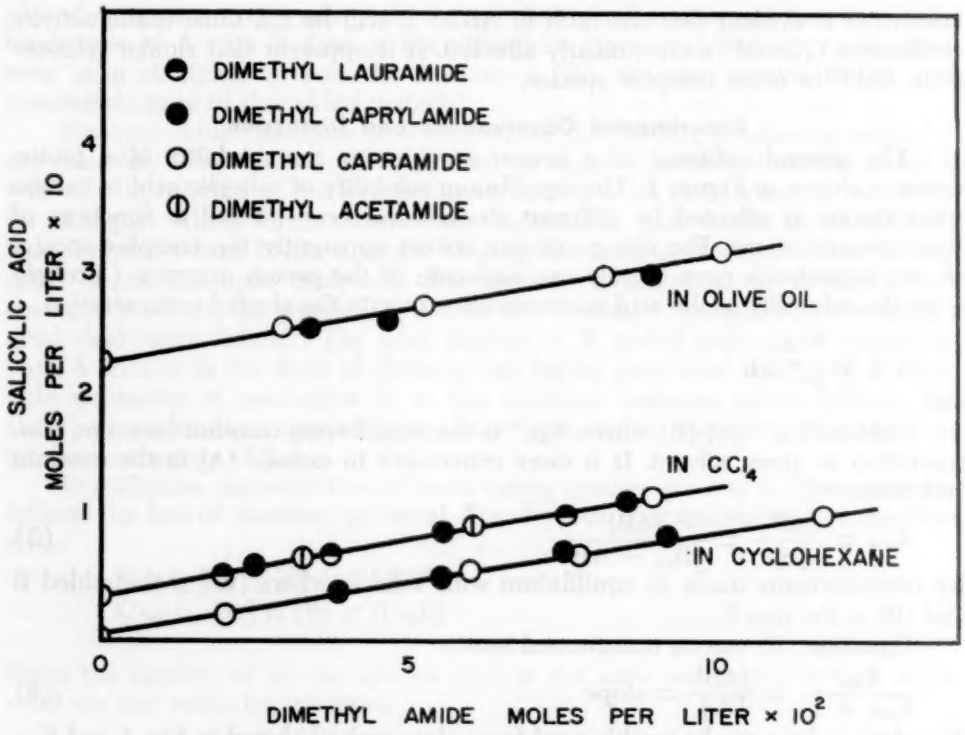

Figure 2.—Dimethyl amide moles per liter × 10^2.

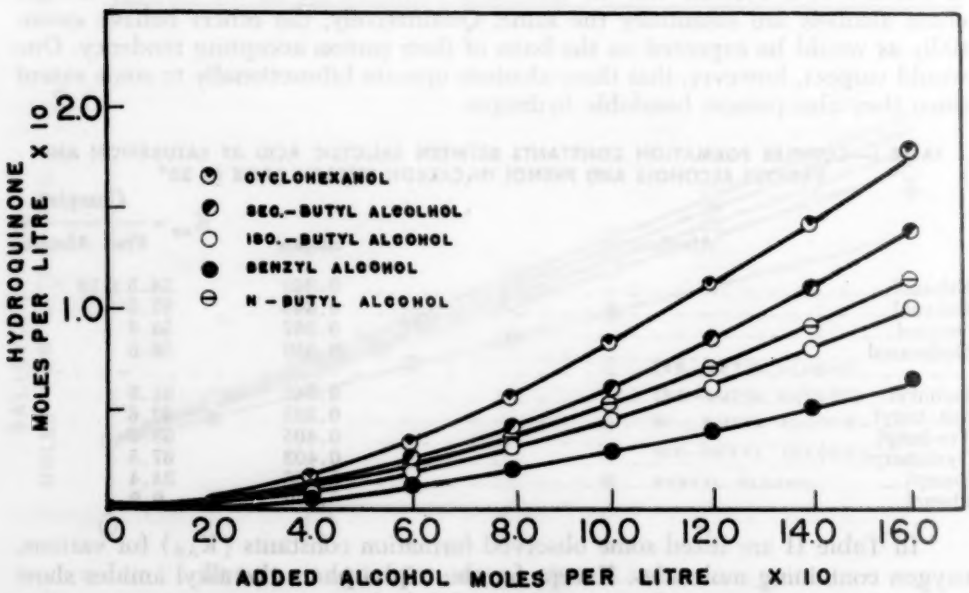

Figure 3.—Phase diagram showing the hydrogen bond formation between hydroquinone and various alcohols.

mined easily since the concentration of the free acceptor in solution is quite small and represents the difference between two large experimentally measured values.

The influence of different solvents on the degree of solubilization is apparent in Fig. 2 for the dialkyl amides in carbon tetrachloride, olive oil, and cyclohexane. The slopes are quite similar and again the chain length makes little difference.

TABLE II—COMPARATIVE FORMATION CONSTANTS OF COMPLEXES FORMED BETWEEN SALICYLIC ACID AT SATURATION AND VARIOUS OXYGEN FUNCTIONS IN CARBON TETRACHLORIDE

Reagent	Salicylic Acid K_{AB}
n-butanol	57.5×10^{-3}
ethyl ether	25.2
diethyl ketone	18.9
ethyl acetate	16.7
n-butyraldehyde	27.3
triethyl phosphate	2,580.0
N,N dimethyl amides	700.0

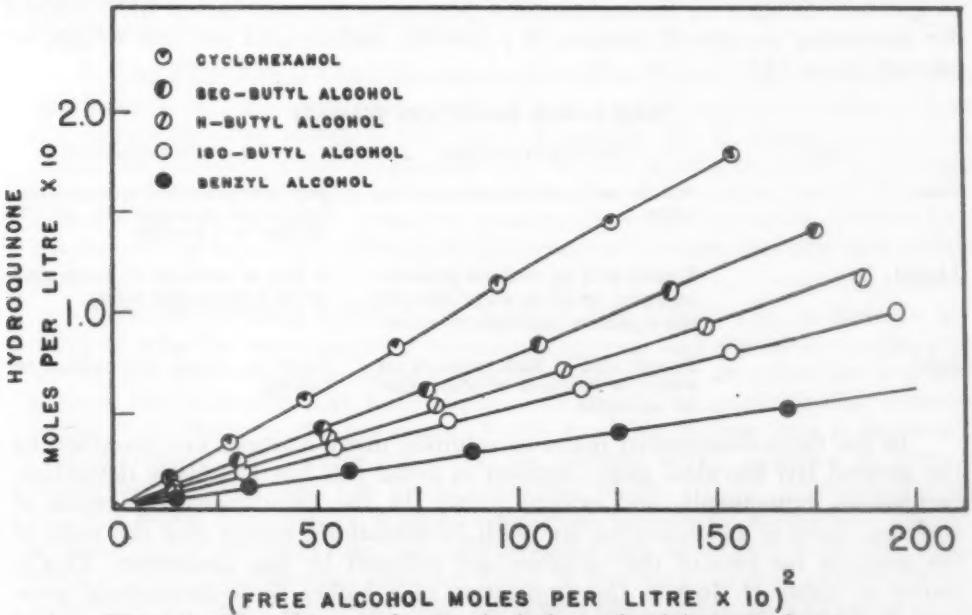

Figure 4.—Phase diagram showing the hydrogen bond formation between hydroquinone and various alcohols.

Fig. 3 and Fig. 4 show the typical behavior for systems which yield predominantly complex species containing two molecules of B. This could take the form of

$$A + 2B \rightleftharpoons AB_2$$

or

$$A_2 + 2B \rightleftharpoons A_2B_2$$

In general the proportion of complex formed in these instances is relatively low at lower concentration of B and solubility plots show an upward curvature as seen in Fig. 3. When the data are plotted as a quadratic function of B as in Fig. 4 a linear plot results. The data shown are for hydroquinone which obviously has two strong donor sites.

FORMATION AND PROPERTIES OF FILMS

RICHARD W. MATTOON

This is a brief review of selected aspects of films—their formation, structure, and some properties—and a few examples of the role of films in the pharmaceutical industry. The nature of surface films is important because many reactions between two or more phases commence at surfaces or interfaces. The thinnest film is one composed of a layer of atoms only one atom thick. A film only one molecule thick, called monomolecular, is the primary structural unit and, because of its importance, much emphasis will be placed on its properties.

Films in the gas, liquid, or solid phase can be formed on a liquid or solid surface as the substrate. Table I gives some examples of these films. The example of gaseous nitrogen on the surface of a powder is the well-known BET method for measuring the specific surface of a powder, surface area per unit weight, or meters^2/gram (1).

TABLE I—FILM PHASES AND EXAMPLES

Film	On Liquid Surface	On Solid Surface
Gas	Stearic acid at low pressure on water	Nitrogen adsorbed monomolecularly and close-packed on the surface of a powder
Liquid	Stearic acid at medium pressure on water, or oil on water showing the common interference colors	A film of moisture on clean glass or on hygroscopic solids
Solid	Stearic acid at high pressure on water, or collodion or other plastic on water	Paint on wood, or coatings on tablets

In the three-dimensional realm of volumes, many relations are described by the general law for ideal gases; applied in detail this law has many deviations, corrections, refinements, and critical points. In the two-dimensional realm of surfaces, there is an analogous law with its deviations, except that the units of the symbols for two of the variables are reduced by one dimension. This is shown in Table II. Just as the application of a higher three-dimensional pressure P, hyperbolically (ideally) reduces the volume, V, of a gas at constant temperature, T, likewise an increasing surface pressure, π, reduces the surface *area*, σ, of a monomolecular film. The product of the two variables in each case gives dyne-cm. or energy in ergs.

TABLE II—COMPARISON OF THE GENERAL GAS LAW

For volumes:	P	V	=	R	n	T
	$\frac{\text{dynes}}{\text{cm.}^2}$	cm.^3		$\frac{\text{ergs}}{^\circ\text{K}}$	no. of molecules	°K
For surface films:	π	σ	=	R	n	T
	$\frac{\text{dynes}}{\text{cm.}}$	cm.^2				

From the measurements of π and σ on monomolecular films of fatty acids, fatty alcohols, sterols, proteins, polymers, macromolecules, etc., and the applications of this surface law, can be obtained the area per molecule, the molecular weight, thickness of the film, which is related to length of the molecule and its orientation of the surface, some features of the structure of the molecular film, compressibility of the molecules, and intermolecular forces (2).

For molecules to form a monolayer on water, they must have at one end *hydrophylic* (water-loving or *oleophobic*) groups such as —COOH or —OH, and at the other end *hydrophobic* (water-repelling or *oleophylic*) groups such as $-CH_2CH_3$. The hydrophylic end may be ionic or non-ionic, but it is attracted to the water surface by polar forces, whereas the hydrophobic end remains out of the water. Intermolecular attractive (cohesive) forces between the molecules cause them to form a film.

One of the very early experiments on films was done by Benjamin Franklin in 1765 in England when he found that one teaspoon of oil was just sufficient to cover a one-half acre pond. This is described in an excellent chapter on interfacial phenomena in Martin's recent book (3).

1. **The Film Balance and Monomolecular Film Phases.** The standard surface film balance for measuring fundamental film properties has been developed from the pioneering work begun in 1917 by I. Langmuir, W. D. Harkins, and N. K. Adam. An example, is that of Harkins (4). It consists of a thermostated trough, barriers (to sweep the water surface clean, to control the surface pressure, and to measure the surface area), a float to measure the surface pressure, and auxiliary attachments to measure surface electrical potential, surface viscosity, and surface tension.

If the film-forming substance is dissolved in a solvent such as benzene and dropped onto the water surface, the solution spreads and the solvent evaporates, leaving the film-forming molecules floating on the water. At a low film pressure, some of the molecules may form circular islands due to intermolecular cohesive forces. This film is in the gas phase. As the available surface area is decreased, thus increasing the surface pressure, the islands finally coalesce to form a homogeneous film called the liquid expanded phase. Higher pressures convert this to a liquid intermediate, a liquid condensed, and then a solid phase. Finally, at even higher pressures the film collapses and one monolayer may fold up on itself to form a bimolecular structure which in turn may fall over or override the monolayer to form a structure three molecules thick. These film phases may be evident from the pressure-area curves of Harkins, for example, and very convincing electron micrographs included in the interesting work of Ries (5, 6).

2. **Electrical Potential and Multilayer Films.** An electrode suspended just above the surface is used to measure the change in electrical potential of the surface of water caused by a film. This electrode can be moved in order to explore the surface. A film in the gaseous phase exhibits potentials which vary considerably between a few millivolts and a hundred, or so, depending upon the film islands under the electrode. However, when the surface pressure is increased sufficiently to form a homogeneous liquid phase, the potential is then sharp and increases steadily with pressure going up to several hundred millivolts (7).

A monolayer film can be transferred to a solid surface by dipping the surface vertically through the film. Blodgett and Langmuir found that under certain conditions monolayers could be deposited one on top of the other to build up a

multilayer thick film (8). Harkins and Mattoon found that each layer of the so-called "X" type of calcium stearate increases the potential of a gold surface about 100 mv. (9). However, if a thin layer of paraffin is first put on the gold, this increment is increased to about 900 mv. per layer.

3. **Viscosity.** One conventional method of determining the viscosity of a three-dimensional liquid is to measure its rate of flow through a tube. Analogously, the viscosity of a two-dimensional film is determined by measuring its rate of flow through a narrow slit in a special barrier of the film balance (10). In general, for the C_{16} to C_{20} fatty acid monolayers in the liquid condensed phase, the family of curves shows a higher viscosity at higher surface pressures, and at the same pressure the longer-chain molecule has a higher viscosity. These viscosities are Newtonian. However, above surface pressures of 21 to 25 dynes/cm. the films are transformed into the solid phase and exhibit rather abrupt increases in viscosity which is non-Newtonian.

4. **Surface Tension.** The surface tension of a liquid is another property which is very sensitive to the presence of a film on the liquid. A recent study shows the precision of measurement of the surface tension of seven pure liquids by various methods (11). A substance is called a *surface active* agent (surfactant) if in solution it concentrates at the surface or interface. The ratio of surface to volume concentration is many-fold.

The surface tension of water is reduced from its value of about 72 dynes/cm. by the addition of pure fatty acids. At comparable concentrations the highly soluble formic acid gives a small reduction, and the longer-chain, less soluble acids give larger reductions in the order of their chain length (12). Small amounts of soaps or detergents added to water reduce its surface tension to the region of 30 dynes/cm. depending on the nature and concentration of the additive.

5. **Contact Angle.** The contact angle between a liquid and solid surface is the angle inside the liquid phase between the liquid and solid surfaces at their line of intersection. This angle can be between 0° and 180°. For water on *clean* glass, it is 0°; for pure water on paraffin, it is about 110°. The contact angle measurement is a simple and yet sensitive method to determine the nature of the surface of a solid and its ease of being wet by a given liquid. If water does not wet a solid (high contact angle), the addition of a wetting agent aids in closer contact between solid and liquid. Wetting agents are commonly surfactants in the detergent class which lower the surface tension of water, lower the contact angle, and aid the liquid in spreading over a solid surface and penetrating the pores of a powder.

Such pores may be regarded as capillaries. The well-known relation for the penetration of a liquid into a capillary is

$$h = \frac{2\,\gamma \cos\theta}{r\,\rho\,g}$$

where h is the height (cm.), γ is the surface tension (dynes/cm.), θ is the contact angle, r is the radius (cm.), ρ is the liquid density (g./cm.^{3}), and g is the acceleration due to gravity (980 cm./sec.^{2}). This is commonly applied to aqueous solutions and glass capillaries where $\theta = 0°$ ($\cos 0° = 1$) and so the factor $\cos\theta$ is omitted. However, for mercury and glass, in spite of γ being the very high value of 520 dynes/cm. (making h large), θ is much larger than 90°, $\cos\theta$ is then negative, so h is actually negative (mercury is depressed in a glass capillary). For water and powders with hydrophobic surfaces, θ is large and pene-

tration is small. The addition of a wetting agent, in spite of reducing γ (and from that, h), reduces θ to such an extent that the product $\gamma \cos \theta$ now increases h or penetration (wetting) of the powder.

6. **Light Reflectivity.** A recent fundamental study of the increase of reflectance of light from a water surface by the addition of a monolayer of a fatty acid showed that the reflectance increases linearly with the square of the number of carbon atoms in the chain (13). The fatty acids studied were myristic (C_{14}), palmitic (C_{16}), stearic (C_{18}), arachidic (C_{20}), behenic (C_{22}), and cerotic (C_{26}). The cerotic acid increased the reflectance 1.3%. It is common knowledge that a well-rubbed, thin film of wax increases the reflectance (shine) of shoes, auto bodies, or coated tablets. Related to this, in the opposite sense, is the effect of a thin film of critical thickness and refractive index coated on optical lenses to *reduce* their reflectance and actually increase their transmission.

7. **Density, Refractive Index, and Friction.** There has been considerable speculation that the density and refractive index of a monomolecular film in a condensed phase may be considerably lower than those properties in the bulk or crystalline phase. However, indirect and some direct measurements by a number of careful investigators show that these constants are nearly the same for the film and bulk phases.

It is well-known that thin films of lubricating materials reduce friction between two solid surfaces. Furthermore, even one monomolecular layer reduces a large fraction of the friction present without the film. In pharmaceutical practice, such films are important in reducing the friction in compressing tablets or in allowing tablets to move in their containers without sticking.

8. **Film Penetration.** If one starts with a monolayer of a substance on an aqueous substrate and then injects into the substrate a different, soluble substance, with the right combination, the molecules of the additive penetrate the monolayer and increase its surface pressure. An example is a monolayer of cetyl alcohol on water with a σ of about 21Å.^{2}/molecule at $\pi = 17$ dynes/cm. (14). At equilibrium with only 10^{-5} M. sodium cetyl sulfate the σ of the alcohol is increased to 120 A.^{2}/molecule at the same π.

The penetration of monolayers by other molecules is highly specific. Sodium cetyl sulfate readily penetrates a monolayer of the *trans* (fairly straight) elaidyl alcohol but not one of the *cis* isomer oleyl alcohol due to its large bend at the central double bond. Sodium cetyl sulfate penetrates a monolayer of cholesterol, but not one of cholesterol acetate nor calciferol. Monolayer penetration has many important biological implications.

9. **Film Permeability for Gases.** A monolayer of some compounds on a water surface reduces its rate of evaporation very markedly due to its low permeability for water. Langmuir and Schaefer performed some of the early experiments on this (15). Meanwhile, many others have continued such measurements. For example, Archer and LaMer found that the rate of evaporation of water was reduced about 10^4 times by a monolayer of a fatty acid, and that the longer the chain the less is its permeability (16). Blank and Roughton measured the rate of uptake of CO_2 through the clean surface of an aqueous substrate (17). They then found that a monolayer of the C_{16} alcohol, C_{16} acid, C_{18} alcohol, and C_{17} amine, in that order, were more and more effective in decreasing the rate. The C_{17} amine reduced it about 60%. On the other hand, monolayers of cholesterol and certain proteins are very permeable to H_2O and CO_2.

These basic studies suggest how thin films of the long-chain fatty acids and especially the fatty alcohols can act as sealers or protective coatings for pharmaceutical preparations to reduce the transmission of undesirable gases into liquids or tablets. Many tablets need protection from H_2O, CO_2, or O_2; the use of films of cetyl or stearyl alcohol is suggestive, at least, as one of the coating ingredients. In Abbott experience, ascorbic acid tablets can be protected from degradation by O_2 and H_2O by a cetyl alcohol film base coating.

10. **Films in Emulsions.** An emulsion can be considered a mixture of two normally incompatible liquid phases made compatible by sealing one of them within spherical monomolecular films of the emulsifying agent. The hydrophylic ends of the emulsifier molecules are oriented toward the aqueous phase and the hydrophobic ends toward the oil phase, regardless of whether it is an oil-in-water (O/W) or water-in-oil (W/O) emulsion.

In general, such films are bonding agents to hold tightly together any two surfaces which otherwise would not adhere. These two surfaces are not necessarily liquid-liquid, as in emulsions, but can be liquid-solid or solid-solid. This use of an intermediate monofilm is very helpful in obtaining an intimate mixture of a hydrophobic powder in a hydrophylic liquid, or vice versa.

11. **Films in Micelles for Solubilization.** As the concentration of many surfactants increases in a solvent, a critical concentration is reached at which many physical properties of the solution or surface show rather abrupt changes in their rates of change. This is the critical micelle concentration (cmc) above which micelles exist in the solution. These micelles are colloidal particles composed of monolayer films of the surfactant arranged into various structures such as lamellar platelets, rod-shaped ellipsoids, or spheres. Kruyt has given a good summary of this (18). Mattoon, Stearns, and Harkins have carried out extensive research on the structure of micelles and the sites of solubilization of oils, and long-chain alcohols (19). Schulman and Riley have made x-ray studies of these colloidal systems (20). Extensive summaries are to be found in the books by McBain, McBain and Hutchinson, and Winsor (21, 22, 23). The use of solubilization in micelles formed by films is an important part of pharmaceutical formulations.

12. **Films in Foams.** In the processing of various solutions containing detergents, emulsifiers, wetting agents, or proteins, the formation of excessive foam is often troublesome. Ways of preventing this are desirable. A thin soap or foam film is composed (like a sandwich) of two parallel monomolecular layers with their hydrophylic surfaces oriented inwards toward each other, between which is a layer of the aqueous solution. The volume fraction of the aqueous phase is about 70% (24).

The mechanism of action of antifoam additives to limit the relative foam volume, or eliminate it completely, is not too well understood. The general idea is that these additives have such properties as to penetrate the film in sufficient concentration to weaken its cohesive forces enough so that it can no longer withstand the pressure of the enclosed gas. The silicone antifoams are very effective at concentrations as low as 10 p.p.m. However, this may concentrate in the final pharmaceutical product above an acceptable limit. Each particular application requires many tests to obtain an antifoam which performs satisfactorily and which is pharmaceutically acceptable. In some cases one of the many fatty acid glycerides meets these specifications.

13. **Films to Reduce the Electrostatic Charge of Powders.** It is quite a common and exasperating experience to process certain fine powders and have them fly around outside the containers between which they are poured, or have them stick tightly to the sides of containers and not fall, even with tapping. This behavior is due to the electrostatic charge built up on the surface of the powder as a result of frictional electrification. The electric potential can build up to several thousand volts and result in a spark discharge causing an explosion or fire under certain conditions.

This phenomenon has been studied by many investigators. At Abbott, we measure the coulombs per gram of powders by letting a known weight flow down a chute into a Faraday cup, of known capacity connected to a Cenco electronic electrometer. From the voltage change, the charge is easily calculated. Powders can be classified by their sign and magnitude. Powders of opposite sign can be mixed and frequently neutralized. Hasegawa has made such measurements on some pharmaceuticals (25).

Several approaches may be tried to reduce these charges. Larger particle size always gives less charge. A moderately strong source of ions in the surrounding air (from polonium, x-rays, gas flame, or electric spark) temporarily neutralizes the charges. Working in high humidities (>80% R.H.) is very effective because the *film* of moisture on the surface is conducting, and this allows the charges to leak off. This film of moisture, desirable in this case, can be made a permanent part of even very fine powders by adsorbing on their surface first a thin film of a substance pharmaceutically acceptable, which is somewhat hygroscopic. For example, a 1% aqueous solution of a Tween may be sprayed on and then dried, or the Tween may be added to the final crystallization liquor if it is aqueous. In our experience, this technique has worked on a variety of powders.

14. **Films in Biological Structures.** Finally, films play major roles in biological structures. Cells are surrounded by membrane films and even inside there are other films separating various compartments. Many workers have investigated the structure of membrane films. Danielli, for instance, shows their structure as a sequence of layers of oriented protein, an oriented monomolecular film of lipids, a layer of interstitial material, an oriented monomolecular film of lipids, and then oriented protein (26). Professor E. N. Willmer of Cambridge University has studied the function of lecithin, cholesterin, and various steroids in the membrane film.

The fundamental studies on monomolecular film penetration and permeability, briefly described earlier, constitute a beginning for the much more difficult understanding of the complex cell membrane film. For information on permeability, the reader is referred to Savson and Danielli (27), and on the involved problems concerning toxic agents and cell membranes, to Albert (28). As an explanation complementary to membrane permeability for the transfer of material in and out of cells, Professor H. Stanley Bennett of the University of Chicago emphasizes another mechanism. Two different cells come into contact; the membranes fuse at this contact, and open on the inside to form one larger cell. Different kinds of cells certainly have different kinds of structures of their membrane films to help account for their highly specific actions.

15. **Film Finale.** The nature and properties of a surface film are very important because this is the site of the beginning of many reactions with another

surface film as they form an interface. These reactions may be chemical, physical, and biological. The application of the knowledge about such films often helps in making better pharmaceutical products.

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THE INFLUENCE OF HYDRATE AND SOLVATE FORMATION ON RATES OF SOLUTION AND SOLUBILITY OF CRYSTALLINE DRUGS

TAKERU HIGUCHI

Considerable attention has been recently directed towards the role of polymorphism in problems of stability and availability of certain dosage forms in which the active constituents are present as crystals. It has been pointed out for example, that the metastable structure leads to a more rapid dissolution of the crystalline drugs, but on the other hand was responsible for the faster physical degradation in suspensions (1). We wish to show that very similar situations exist in many instances for systems which form hydrates and solvates. Since the differences in the free energy levels of these additional compounds are generally greater than those involving purely crystalline modification, solubility behaviors usually show larger variations.

A surprising number of organic compounds having medicinal value show a tendency to form solvent addition compounds. Many drugs such as quinine, sulfonamides, steroids, barbiturates, xanthines, tetracyclines, etc., exhibit a strong tendency to form discrete hydrate structures. Much less is known concerning formation of solvates with organic solvents but the tendencies of alkaloids and steroids to crystallize out with solvent are common knowledge. Despite their frequent occurrence and their importance in modifying solubility behaviors, no serious effort seems to have been made to utilize particularly the organic solvent adducts in developing superior pharmaceutical forms.

In the present study we have studied the rates of dissolution of the anhydrous and hydrated forms of theophylline, caffeine, glutethimide and cholesterol. Two solvents of 9-fluorohydrocortisone acetate were also investigated. In addition thermodynamic determinations were made on the two forms of glutethimide and theophylline.

Theoretical Considerations

Dissolution Rate. Noyes and Whitney (2) have shown that the rate of dissolution of solids is directly proportional to the concentration gradient when the surface area of the dissolving material changes negligibly for systems yielding only a single species in solution.

In their equation (eqn. (1)), C_s is the concentration of the saturated solution and C_t is the amount dissolved at time t. The k in this

$$\frac{dC}{dt} = k\,(C_s - C_t) \qquad (1)$$

equation has been investigated by many workers and has been shown to be dependent on many factors; on the surface area of exposed solid, the intensity of agitation, the temperature, the size and shape of particles, the apparatus used and the diffusion constant of the dissolved material. It is evident from the equation that for dissolution process occurring in media where $\frac{C_t}{C_s} << 1$, such as

may be found during absorption of uncharged drugs via the oral route, the solubility term C_s, is the major determining factor. This same relationship holds whether anhydrous forms of hydrates are being dissolved in water.

Dissolution behaviors of solvated solids in water have not, to the author's knowledge, been treated mathematically. Since it appears that these molecular compounds may possess such significantly higher rates of solution as to be of pharmaceutical importance, the equations relating some of the factors involved have been derived. If we take a crystalline substance which dissociates as follows in water:

$$A{:}nB \longrightarrow A + nB$$

and which follows the solubility product principle of

$$C_A\, C_B{}^n = K_{sp}$$

the rate of dissolution under constant stirring and geometric conditions can be written as

$$\text{Rate of dissolution} = G = \frac{dC_A{}^\bullet}{dt} = kD_A(C_A - C_A{}^\bullet)$$

$$= \frac{1}{n}\frac{dC_B{}^\bullet}{dt} = \frac{kD_B}{n}(C_B - C_B{}^\bullet)$$

where $C_A{}^\bullet$ and $C_B{}^\bullet$ refers to the concentration of the two species in the bulk of the solution, C_A and C_B their respective concentrations at the immediate crystal surface, D_A and D_B the respective diffusivity and k the combined geometric and agitation factor. For our thinking we can take A to be the drug component (e.g. steroid) and B the organic solvent (e.g. amyl alcohol).

For the case $n = 1$ and $D_A \cong D_B$ the above relationships yield a very simple solution of

$$G = \frac{dC_A{}^\bullet}{dt} = kD(\sqrt{K_{sp}} - C_A{}^\bullet) \qquad (2)$$

having a form very similar to equation (1). It is evident that $C_A{}^\bullet$ can build well above the solubility of A itself in water to yield crystalline deposits unless the solution is continually diluted or the drug is absorbed.

For the case $n = 1$ and $D_A < D_B$ the end relationship is still relatively simple.

$$G = \frac{dC_A{}^\bullet}{dt} = \frac{kC_A{}^\bullet}{2}\left[\sqrt{(D_B - D_A)^2 + \frac{4K_{sp}D_AD_B}{C_A{}^\bullet}} - (D_A + D_B)\right]$$

This leads to a zero rate only when $C^{\bullet 2} = K_{sp}$ as expected and does not represent a first order approach to saturation as is the case for both (1) and (2).

Under average conditions these equations predict that the rates of solution of these solvates would be very much greater than that of parent drug. This would be particularly true if the solvating agent is significantly water soluble.

Thermodynamic Relationships. From the preceding discussion it is apparent that the rates of solution of drugs and other organic solids in aqueous media are intimately dependent on the limiting solubilities for anhydrous and hydrate species and solubility products for solvated solids. These are essentially equilibrium values and are dependent on the free energy changes involved in the dissolution process. Thus we can write

$$A(z) \overset{K_s}{\rightleftarrows} A \text{ (solution) } H_2O \qquad \text{anhydrous} \qquad (3)$$

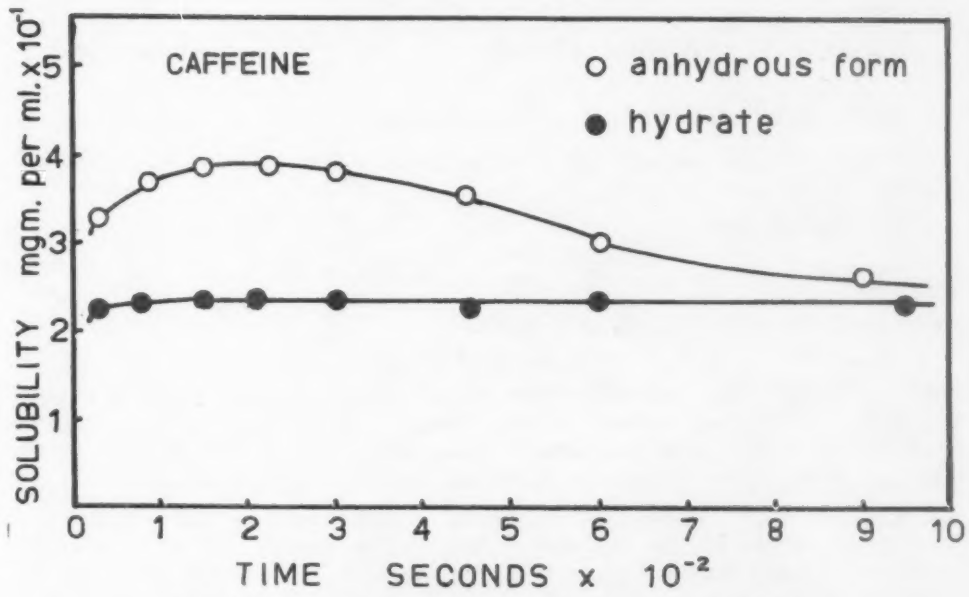

Figure 1.—Solubility of caffeine in water versus time at 28°C.

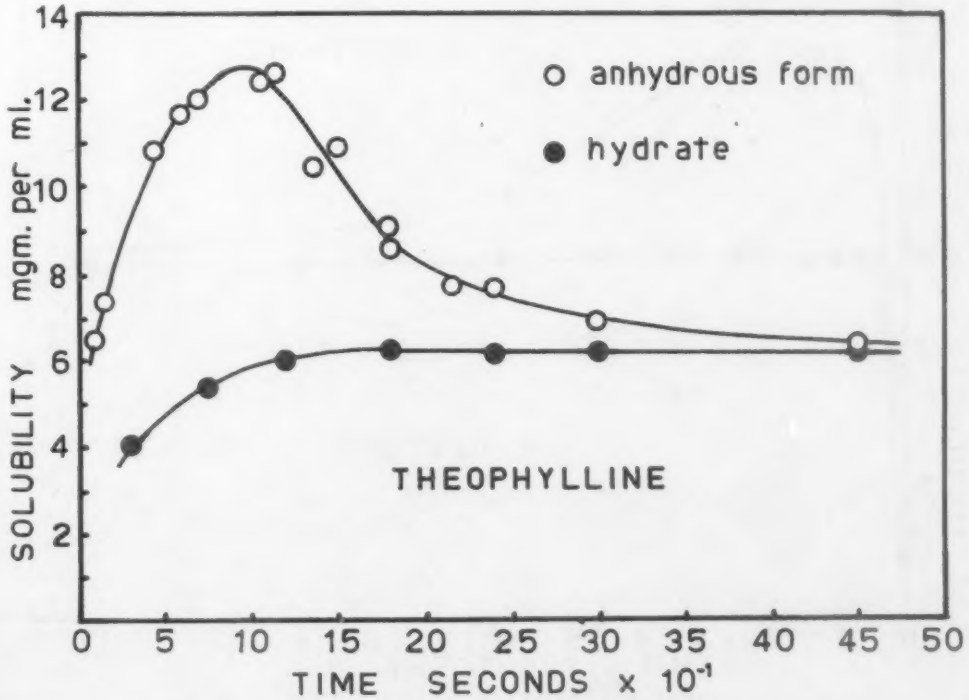

Figure 2.—Theophylline solubility versus time at 25°C in water.

$$A : xH_2O\ (s) \overset{K_s}{\rightleftarrows} A\ (\text{solution})\ H_2O \qquad \text{hydrate (4)}$$

$$A{:}nB \overset{K_{sp}}{\rightleftarrows} A\ (\text{solution})\ H_2O + (B(\text{solution}))._n \qquad \text{solvate (5)}$$

The equilibrium constant can be given as the molar solubility K_s for the first two and as the solubility product for the third.

It is evident that

$$\Delta F = RT \ln \frac{K_s\ (\text{hydrate})}{K_s\ (\text{anhydrate})}$$

corresponds to the free energy of hydration

$$A\ (s) + x\ H_2O \longrightarrow A{:}xH_2O\ (S).$$

Since solubilities can be readily measured at several temperatures it is evident that both enthalpy and entropy changes corresponding to these processes can be easily determined. These data are of some theoretical interest relative to the information they provide concerning the structures of these solids.

The free energy change corresponding to the process shown for the equilibrium (5) above for the solvated system can be readily evaluated from the solubility of the solvated A in pure B, the solubility of unsolvated A in B, the solubility of the same unsolvated A in water and the activity coefficient of B in

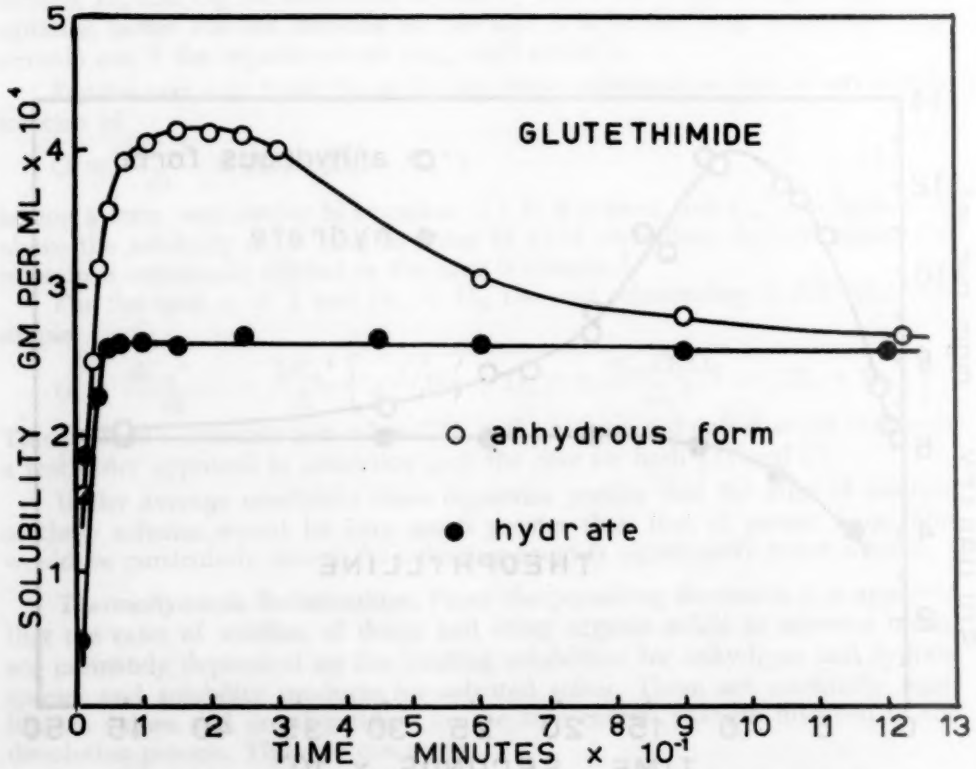

Figure 3.—Solubility of glutethimide at various time intervals at 25°C in aqueous alcoholic solution.

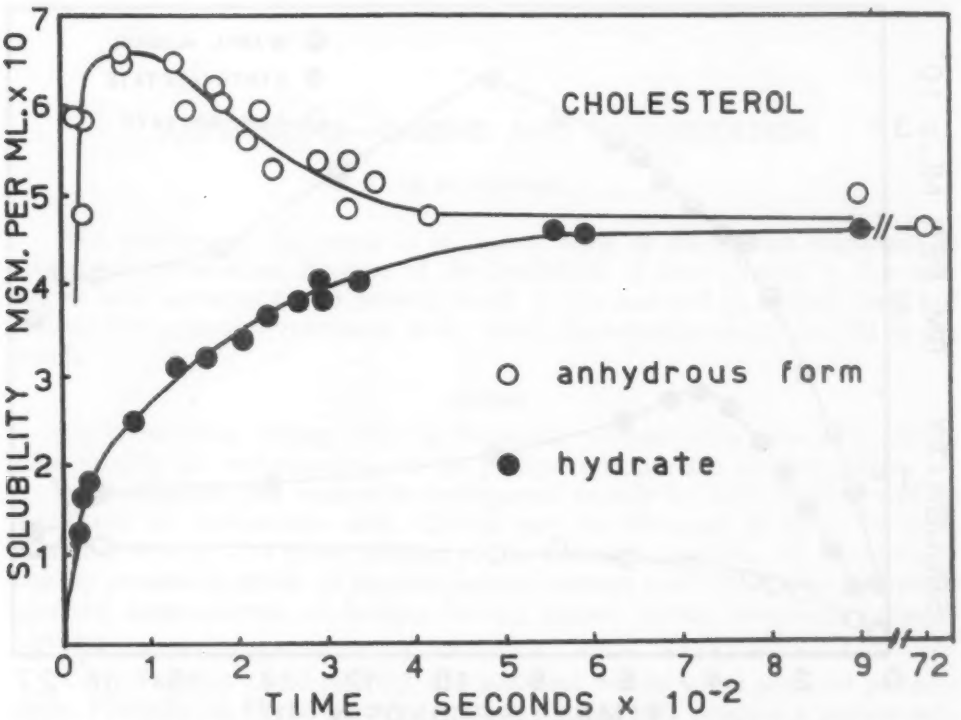

Figure 4.—Solubility of cholesterol in an alcohol-glycerine mixture at 25°C versus time.

water. It suffices to say at this point that for the type of systems with which we are normally concerned (5) represents a far greater free energy change than (3) or (4). Thus from the standpoint of both kinetics and thermodynamics it would appear that solvates of this type merit closer attention as means of attaining faster and greater dissolution.

Experimental Observation and Discussion

The influence of hydrate formation on the rate of dissolution of caffeine, theophylline, glutethimide and cholesterol are shown in Figs. *1*, *2*, *3* and *4* respectively. In these runs the amount of the solid studied was usually more than five times that necessary to produce saturation. Determinations were carried out under conditions of essentially constant agitation and in a flask fitted with a thermostated water jacket. Although no great pains were taken to achieve identical particle size, no readily observable differences were noted among the samples studied. The respective plots show the concentration of the drug achieved in solution as a function of time.

It is apparent from the plots that anhydrous crystals and the solution attained equilibrium state only for a short time, as indicated by the plateau, because of rapid nucleation of, and conversion to, the less soluble hydrate. Caffeine and theophylline exhibited this behavior in water (Fig. *1* and *2*), while glutethimide showed similar behavior in a solution of ten per cent alcohol in water (Fig. *3*). Similar results would be expected in pure water since the activity of water in solution was not materially changed. Figure *4* shows the same type curve for anhydrous cholesterol in a glycerin-alcohol system (containing about 5 per cent

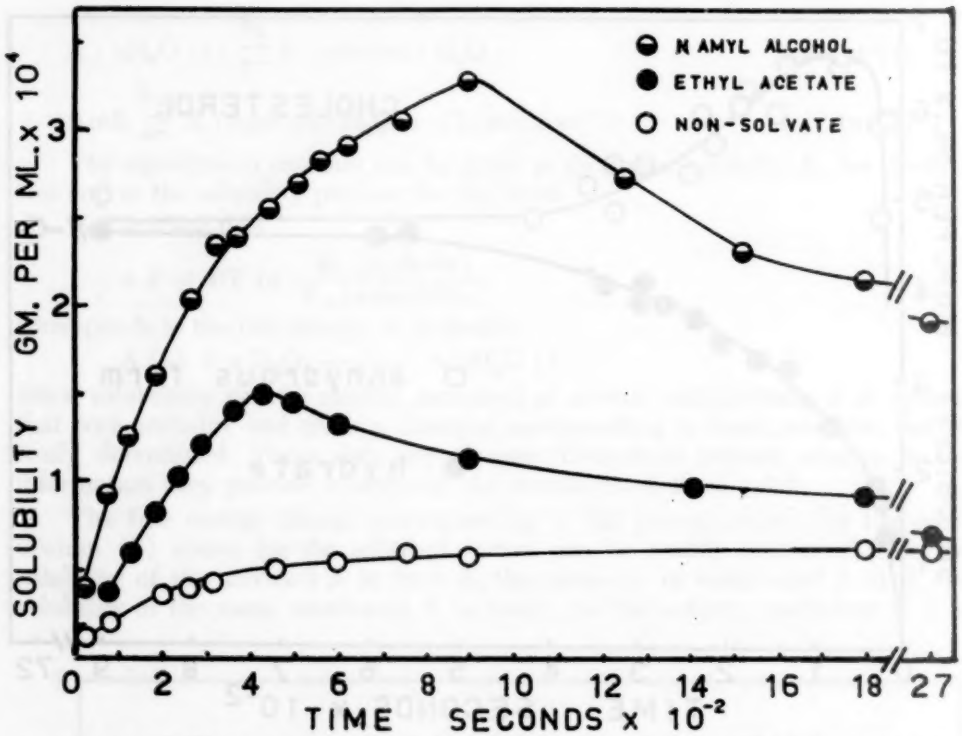

Figure 5.—Solubility of three forms of fludrocortisone acetate as a function of time at 20° C.

water). Alcoholic solutions were used in these instances to permit higher concentrations of the drugs. In separate experiments it was possible to retard the nucleation of anhydrous theophylline to the hydrate significantly by addition of gelatin to the water.

The dissolution behavior of only organic solvents of 9-fluorohydrocortisone acetate (fluodrocortisone acetate) has been determined to date. As expected these exhibited relatively high rates of solution. The concentration build up for an ethyl acetate solvate and n-amyl alcohol solvate is shown in Figure 5. The normal amyl alcohol solvate shows at least five times the solubility of the non-solvated species, while an apparent two fold increase is realized with the ethyl acetate solvate. The existence of these species was evidenced by their characteristic x-ray patterns and loss of weight on drying. They both appear to be mono-solvates.

Since the initial peak values exhibited by the hydrate plots correspond to the solubility of the corresponding solid species, it is possible to calculate the differences in the thermodynamic values for these systems. This has been done for glutethimide and theophylline, the general approach being the same as that described by Higuchi *et al* for polymorpha (3).

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SUSPENSIONS—CAKING AND SEDIMENTATION

E. N. HIESTAND

The purpose of this paper is to review some of the factors important to suspension formulation. Because of the limitations of time allotted to this subject, it will be necessary to present much of the material in outline form but provide the necessary references from which interested workers may fill in the details.

Caking

By considering caking prior to discussing sedimentation, one may obtain more rapidly an understanding of the preferred suspension characteristics.

Any sediment that cannot be redispersed readily by mild shaking will be considered an undesirable cake. Caking may be discussed in terms of three related processes: (1) Close packing of the sediment particles, (2) Solid inclusion by crystals at points of particle-particle contact, and (3) Fusion of crystals resulting from growth of bridges having crystal lattice continuity between particles.

Close Packing. Close packing of a sediment results when peptized particles settle. Flocculation of the particles prior to settling may produce a porous sediment. Overbeek (1) states that ". . . a flocculated suspension is easily repeptized, it is very difficult to redisperse the compact sediment of a stable suspension. . . . The sediment is so compact that the particles can only be attacked by hydrodynamic motions layer by layer which evidently is a slow process." This brief statement contains the semantic trap that has misled many investigators early in their formulation careers, i.e., the word "stable." In Colloid Science *stable* refers to particles that do not flocculate. In Pharmacy stable implies little or no settling. These two connotations lead to confusion because in practice the methods for producing peptized colloidally stable suspensions will be diametrically opposite to those producing flocculated pharmaceutically stable susensions.

The loose character of the sediment of the flocculated suspension has been considered in terms of the ease of redispersion by shaking. Overbeek (1) comments that for coarse particles the colloidally stable suspension settles to form a close packed sediment that is hard to redisperse; but a flocculated suspension forms a large sedimentation volume and is more readily redispersed. Figure 1 illustrates these two cases. These are coarse suspensions where the large particle size accounts for the rapid settling. Overbeek (1) also comments on the advantage of having large particles in the sediment because of the force acting to dislodge the particle as liquid flows around it. If a particle resting on top of a surface is exposed to the shearing action of a liquid in laminar flow, the average velocity of the vehicle flowing past the particle is directly proportional to its diameter; also, the force acting on the particle due to liquid flow is given by Stokes law and is directly proportional to the particle diameter. Therefore, the force acting to dislodge a particle is proportional to the square of the particle diameter. The sediment with the largest possible sedimentation volume is the closest approach one can make to this ideal situation in a practical case.

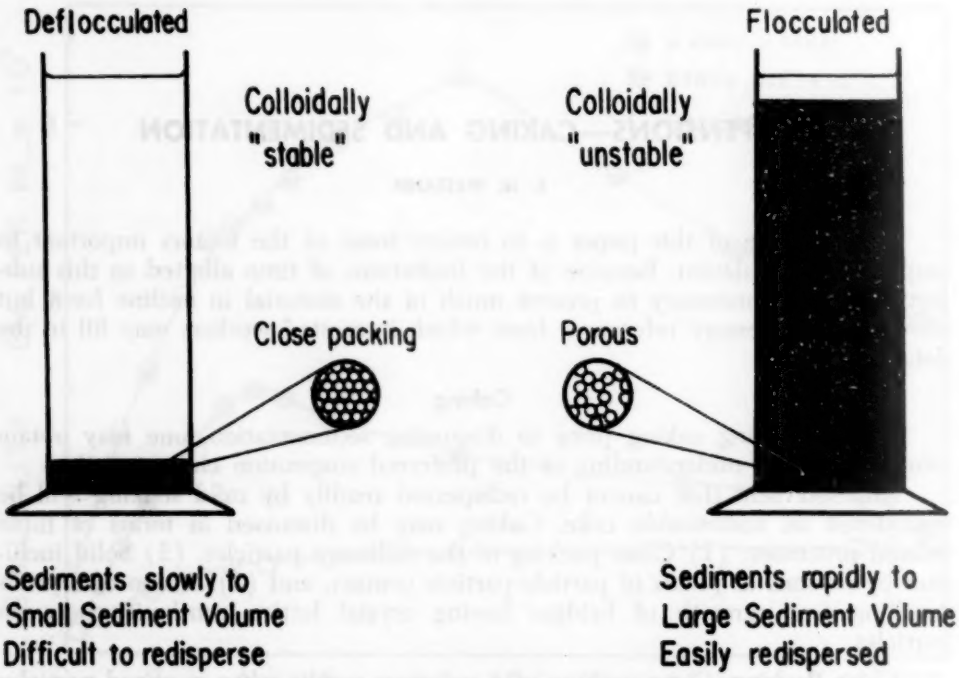

Figure 1.—Comparison of coarse dispersions peptized and flocculated.

Solid Inclusion. Solid inclusion results when particles in contact grow. Particles may grow in a suspension because of the differences in solubility of large and small particles. If this growth occurs at points of contract of two particles, a mechanical bonding due to increased opportunity for dispersion forces to act may result, e.g., when the face of one crystal grows around an edge or end of another crystal. If the sediment is close packed this mechanical "lock-and-key" bonding may contribute greatly to the difficulty in resuspending the cake. Excessive growth would be required before this effect would be significant in a very porous sediment.

Growth with Crystal Lattice Continuity. This type of growth is a special case similar to solid inclusion. However, special orientation of the two particles is required so that growth between the particles may occur without disrupting the lattice structure of either particle. The orientation requirements are the same as for crystal twinning. Obviously, this type of growth actually fuses the two particles into one; and if this action extended throughout a sediment structure; it would produce a very rigid cake. However, the very special orientation requirements make this fusion improbable. Assuming it does occur, the porous sediment with fewer particle contacts would be the preferred form.

Crystal growth in suspensions results from solubility differences. This may occur isothermally if the particle size range is large, and estimates of this effect are obtained from Kelvin's equation or Knapp's (2) equation. Temperature cycling may produce growth because of changes in solubility with temperature. Obviously the more soluble the solid, the greater this problem may become. Of course, polymorphic changes should be avoided if possible.

The a priori considerations above lead to a universal conclusion, viz., for coarse suspensions a large sedimentation volume is preferred in order to avoid the problem of caking. That this may be produced by flocculating a suspension has been recognized for many years

Sedimentation

It is tempting to dispose of the subject of sedimentation by a simple statement: For coarse suspensions, sedimentation will occur unless very special measures are taken to prevent it. This is true because the sedimentation rate becomes significant when the density difference between the particle and the vehicle, $\Delta\rho$, is approximately equal or greater than 0.02 g./ml. and the diameter, d, of the

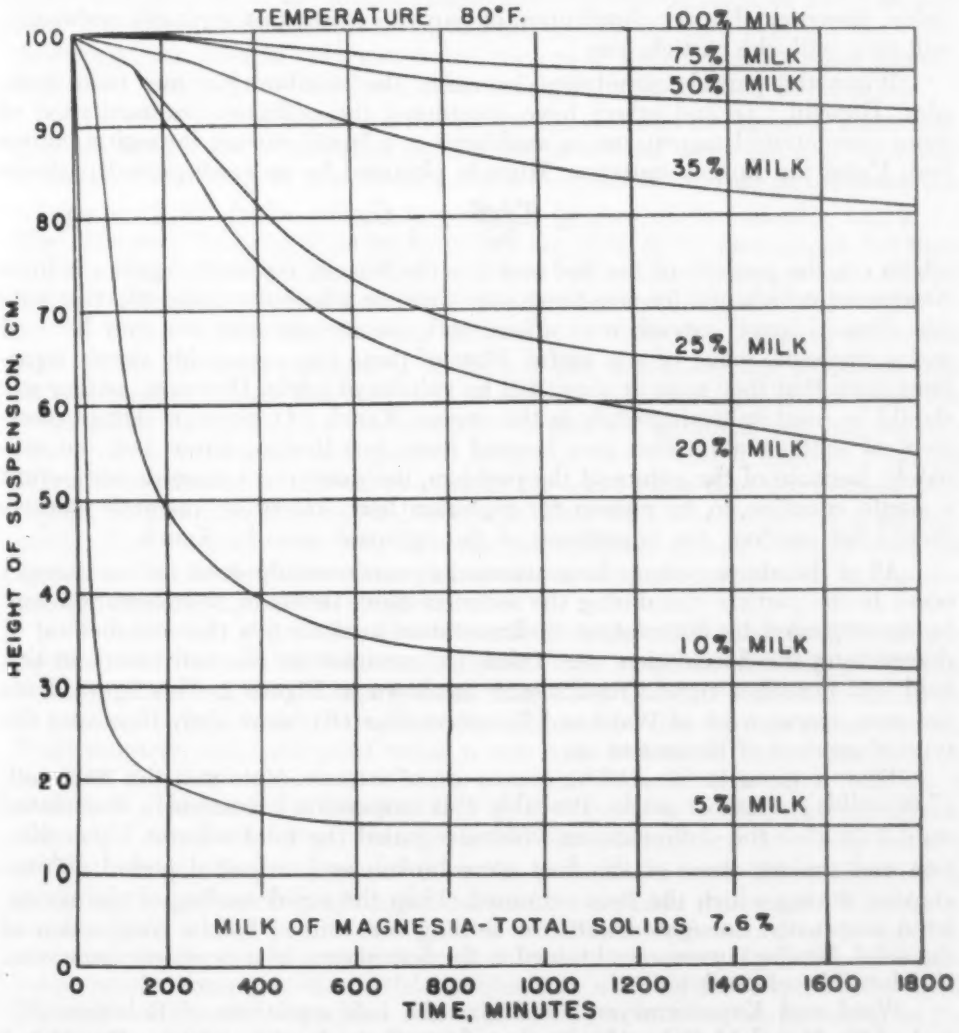

Figure 2.—Settling curves of milk of magnesia at various degrees of dilution. From: Ward and Kammermeyer, "Sedimentation in the Laboratory," Ind. Eng. Chem., 32, 622 (1940). Reproduced with permission from the American Chemical Society.

particle is $\geqq 0.5\ \mu$. Of course, these numbers are based on arbitrarily selected criteria and cannot be considered absolute. To understand these criteria, it is necessary to consider more carefully the process of sedimentation.

The simplest case to describe mathematically is the sedimentation of a spherical particle, large in size compared to the molecules of the Newtonian vehicle, and unhindered by other particles. Combining the gravitation force with Stokes law, one obtains

$$v = \frac{2r^2\Delta\rho g}{9\eta} \qquad (1)$$

where v is the velocity, r is the radius, $\Delta\rho$ is the density difference, g is the gravitational constant, and η is the viscosity.

If the vehicle is non-Newtonian it is possible to replace η with its effective value. However, if a size distribution of particles exists, this stochastic value of η will vary with the particle size.

When the particle population increases, the situation becomes more complex. Higuchi (3) and others have considered the collective sedimentation of more concentrated suspensions as analogous to a liquid moving through a porous bed. Using the Kozeny equation, Higuchi obtained for mono-dispersed particles

$$v = \frac{r^2\Delta\rho g}{9\eta k} \cdot \frac{\epsilon^3}{1-\epsilon} \qquad (2)$$

where ϵ is the porosity of the bed and k is the Kozeny constant. Again η is for a Newtonian vehicle and for non-Newtonian's will be a function of the effective pore size. Since a "pore" extends over a long path, an average pore size may be used and a stochastic value of η is useful. Plots of these two reasonably simple equations show that they cross at about 10% by volume of solids. However, neither one should be used indiscriminately in this region. Kynch (4) gives an elegant treatment of sedimentation that goes beyond these two limiting cases; but, unfortunately, because of the nature of the problem, the more exact cases do not permit a single equation to be chosen for inclusion here. However, research workers should not overlook the importance of the approach used by Kynch.

All of the above systems have assumed a pseudo-steady state; i.e., no changes occur in the particle size during the sedimentation. However, sedimentation may be accompanied by flocculation. Sedimentation analysis is a classical method of determining the flocculation rate. Oden (5) summarizes the early work in this field and describes typical results such as shown in Figure 2. This figure, from the more recent work of Ward and Kammermeyer (6), more aptly illustrates the type of product of interest to us.

Three regions in the settling curves are of interest. Note that the 100% milk (7.6% solids) does not settle. Probably this suspension existed in a flocculated state such that the sedimentation volume equaled the total volume. Upon dilution and shaking some of the flocs were broken and an initial period of time elapsed during which the flocs reformed. Then the rapid settling of the flocculated suspension dominated until the settling was limited by the compaction of the solid. Similar curves are obtained if the flocculation of a peptized suspension is induced by electrolytes.

Ward and Kammermeyer summarize the rate equations of Robinson (7) and of Egolf and McCabe (8) for describing the sedimentation of a flocculated suspension. Also, these authors make use of the ratio of the ultimate height after settling, Hu, to the initial height, Ho, which is called the sedimentation volume

and may be designated F, i. e., F = Hu/Ho. Dintenfass (9) prefers to use the volume ratios, F = Vu/Vo. He extends the usefulness by defining the degree of flocculation, β, as $\beta = F/F_\infty$ where F_∞ is the value of F for a completely peptized suspension. This is an excellent reference point because the close packed structure will occupy the minimum volume possible; and any larger sediment volume is a result of flocculation .

Flocculated Suspensions

The use of water as a flocculating agent in oil base paints to prevent hard cakes as sediments was described in 1930 by Rhodes and Jebens (10). Zettlemoyer (11) states that less than a monolayer of water may produce flocculation of some systems. Similar results have been obtained by Wiegand and Venuto (12) with gasoline as the flocculating agent for a carbon black in water suspension. The use of hydrocolloids as flocculating agents has been practiced for many years, e.g., van Iterson (13) mentioned the use of starch in 1938. More recently Jack (14) and Martin (15) have given examples of flocculated formulations.

The effect of flocculation on the suspension is shown in Figure 3. These samples are from a study conducted by the author several years ago and represents a case of flocculation by a surfactant. Note the gradual increase in sedimentation volume until the entire volume is occupied by two of the samples, i.e., $F \geq 1$ The difference between these last two does not show in the photograph but there is an increase in yield value as the surfactant concentration is increased. According to Dintenfass (9) this last sample is a compressed sediment.

In Figure 4 the same materials are used but, following the work of Dintenfass (9) for the cases where $F \geq 1$, some of the suspension was separated from its equilibrium vehicle and this vehicle added to another part of the same suspension. By this procedure the normally compressed sediment now has the necessary room to become an expanded sediment and F and β may be obtained. When the sediment is allowed to expand, the yield value does not increase very rapidly as it did for the confined sediment. This work was done with a medicament whose concentration was at a normal teaspoon dosage level. It does not represent the final product since preservatives, etc., are not present in the suspensions shown in Figures 3 and 4.

So far in this discussion, characteristic sedimentation rates have been considered, and flocculation has been proposed as a means of avoiding sedimentation by increasing F to values greater than 1. An alternative solution would be to produce a vehicle with a sufficiently high yield value to stop sedimentation. Unfortunately, the term yield value is not well defined. If this approach is to succeed, it is important to produce a true yield value that is not a function of shear-rate. This may be characterized as a suspension vehicle that undergoes very slow or no relaxation when subjected to a stress below its elastic limit. A rapidly relaxing material would allow the particles to settle. Mattocks (16) is studying these properties of suspensions with a suitable rheometer. Whether or not a vehicle with a yield values is truly a different approach than flocculating the medicament particles may depend on one's view point. Probably any yield value results from particle-particle interactions obeying the same fundamental principles. However, the added factor of hydrogen bonding contributing to the yield value produced by a soluble hydrocolloid must not be overlooked.

From the above considerations, one is led to the conclusion that the fundamental principles of colloid science dealing with the electric double layer and

Figure 3.—Shows various degress of flocculation produced by a surfactant. Bottle at right contains some unsettled fines but most of the solid is at the bottom. On the left, sediment in two bottles occupies entire liquid volume. Sediment with 5% surfactant exhibits a high yield value. Foam tends to obscure the interface.

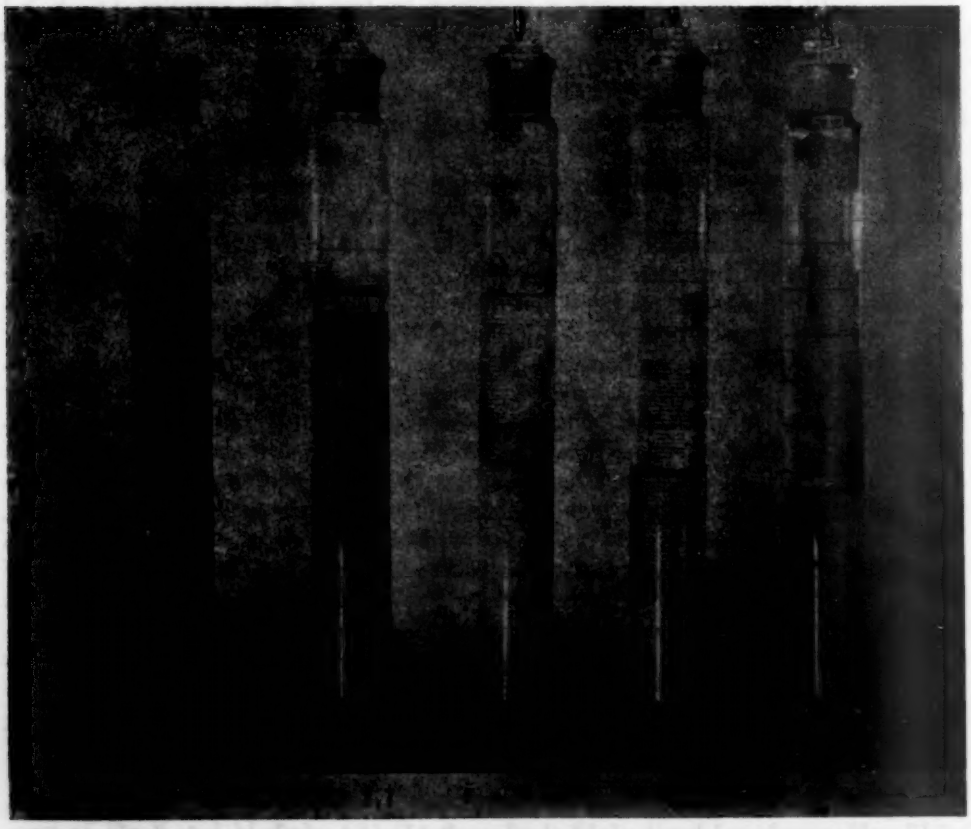

Figure 4.—Shows various degrees of flocculation produced by a surfactant. Sediment from the peptized suspension (F_∞) occupies very small volume. Added equilibrium vehicle permits the degree of flocculation to be evaluated for cases where $F > 1$.

the London-van der Waal's forces are basic information useful for suspension formulation. The reader should refer to standard texts of *Colloid Science* (17, 18) and to more advanced treatises (19, 20) for this material.

Before closing this discussion, the author would like to discuss an interesting series of papers on the subsidence of flocculated slimes by Smellie and La Mer (21) which describe a technique of flocculation that seems to provide exactly the type of flocculation desired in pharmaceutical suspensions. These authors were interested in producing a porous sediment in order to obtain rapid filtration. They found that when flocculation is produced by electrolyte addition alone, the sedimentation volume is small. Exceptions to this are known but as a general rule the best suspensions are not produced by simple electrolyte flocculation. They found that small additions of hydrocolloids produced a very porous sediment. Figure 5 shows the narrow range of flocculant concentration producing the most porous sediment as judged by the filtration rate. Figure 6 diagrammatically illustrates the mechanism. Note that flocculation resulted only when an uncoated area of one particle contacted the coated area of another particle. The evidence for this mechanism is the excellent correlation they obtained with their equations based on this mechanism. They assumed that the probability of adhe-

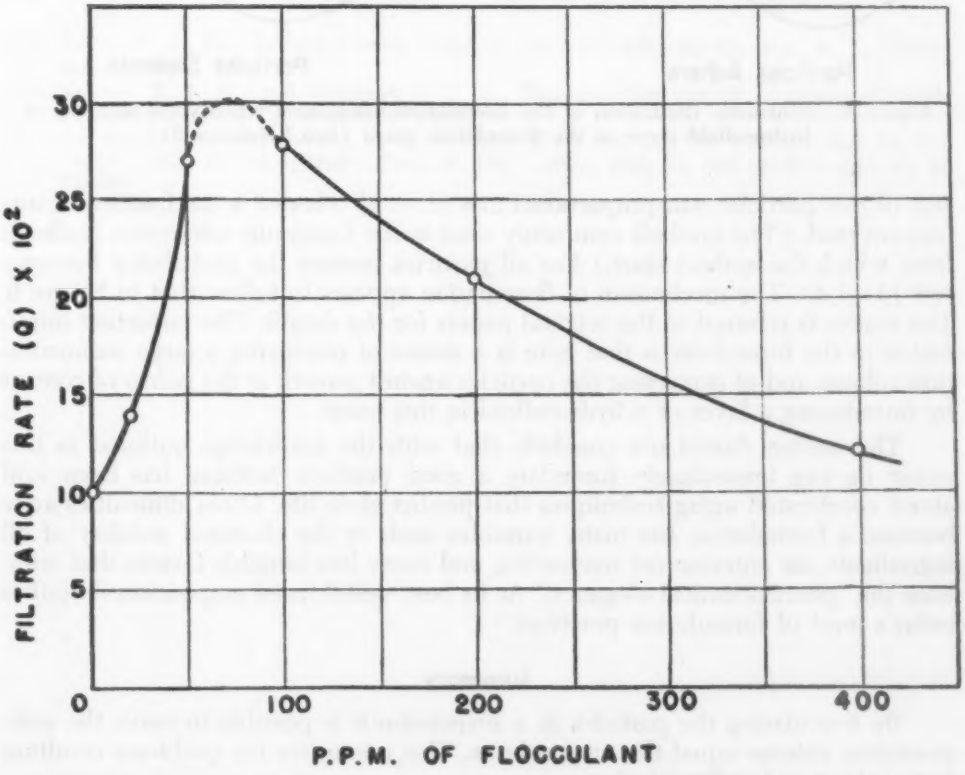

Figure 5.—Shows the variation of the "refiltration rate" in cc. per second *versus* the concentration of Lytron 886 (product of Monsanto Chemical Company) in parts per million. Each sample contained 1000 p.p.m. of added $CaCl_2$. From: Smellie and La Mer, "Flocculation Subsidence, and Filtration of Phosphate Slimes, VI., J. Colloid Sci., *13*, 589 (1958). Reproduced with permission from Academic Press, Inc., N. Y.

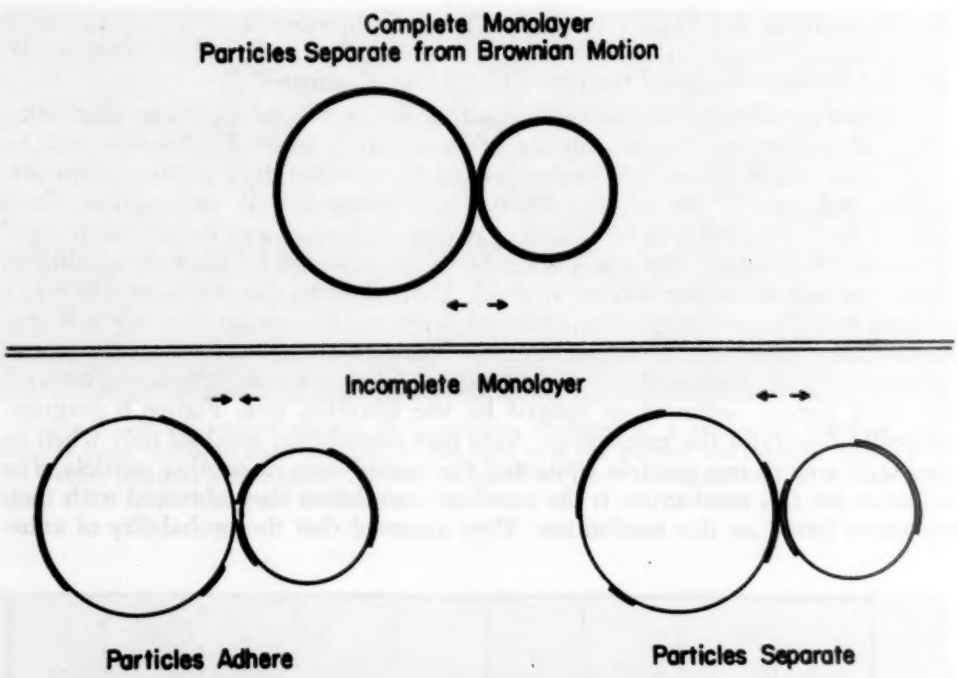

Figure 6.—Schematic illustration of the flocculation mechanism when small amounts of hydrocolloid serve as the flocculating agent (See Reference 21).

sion of two particles was proportional to $\theta\ (1 - \theta)$ where θ is the fraction of surface covered. (The symbols commonly used in the Langmuir adsorption isotherm from which the authors start.) For all particles present the probability becomes $N^2\theta\ (1 - \theta)$. The mechanism of flocculation appears to follow that in Figure 6. The reader is referred to the original papers for the details. The important implication to the formulator is that here is a means of producing a large sedimentation volume and of protecting the particles against growth at the points of contact by introducing a layer of a hydrocolloid at this point.

The novice should not conclude that with the knowledge outlined in this paper he can immediately formulate a good product. Nothing has been said about accelerated aging techniques that predict shelf life. Other difficulties arise because a formulation has many variables such as the chemical stability of all ingredients, air entrainment tendencies, and many less tangible factors that influence the "pharmaceutical elegance." At its best, enlightened empiricism describes today's level of formulation practices.

Summary

By flocculating the particles in a suspension it is possible to make the sedimentation volume equal the total volume. This minimizes the problems resulting from caking and sedimentation.

ACKNOWLEDGMENTS

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ABSORPTION FROM THE GASTROINTESTINAL TRACT

LEWIS S. SCHANKER

When a drug is administered orally, and dissolves in the fluids of the gastrointestinal tract, it may pass into the bloodstream rapidly or slowly depending on the ease with which it can cross the epithelial lining of the stomach and intestine. In considering the permeability of the gastrointestinal epithelium to drugs, it is helpful to have in mind some of the important ideas about the nature of the cell membrane that have evolved during the past sixty years. The classical studies of Overton and of Collander and Bärlund on the permeability of plant and animal cells to organic compounds led to the view that the cell boundary is essentially a lipid-like layer interspersed with small water-filled channels; nonpolar substances penetrate the boundary by dissolving in the lipoid phase, whereas polar molecules penetrate only if they are small enough to diffuse through the aqueous channels. Later workers recognized that the cell membrane is more than a simple lipoid sieve; they demonstrated the active nature of the membrane in transporting lipid-insoluble subtrates required by the cell. For example, certain sugars and amino acids enter the cell by processes which exhibit specificity, saturability, and a requirement for energy.

Until recently, studies of the mechanism of gastrointestinal absorption have been concerned mainly with the complex, active processes responsible for the absorption of monosaccharides, amino acids, fats, and certain inorganic ions. So much attention has been directed toward these investigations that many workers have failed to consider the early concept of diffusion across a lipid-like membrane as a possible explanation for the absorption of drugs and other foreign organic compounds.

In applying the lipoid membrane hypothesis to the gastrointestinal absorption of drugs, it is necessary to take into account that most drugs are weak organic acids or bases, which exist in solution as a mixture of the ionized and unionized forms. This complicates the problem of describing the passage of drugs across a membrane, since usually only the unionized forms are lipid-soluble. The proportion of drug in the unionized form depends on the dissociation constant of the compound and on the pH of the medium; consequently, to analyze drug absorption in terms of the lipoid membrane thesis, it is necessary to know the dissociation constant of the drug as well as the lipid/water partition coefficient of the unionized drug form.

Absorption of Drugs from the Stomach

To investigate gastric absorption, drugs dissolved in 0.1 N HCl solution were placed in the doubly-ligated stomach of anesthetized rats, and the degree of absorption was estimated from the amount of drug remaining in the stomach after one hour. Since weak acids exist in the acidic gastric contents mainly in their lipid-soluble, undissociated form, and most weak bases are highly ionized,

only the acidic compounds should be absorbed. In accord with this view, ready absorption was observed for all of the acidic drugs except the strong sulfonic acids, which are ionized even in solutions of low pH. Thus, salicylates, phenols, and barbiturates were absorbed, but sulfonic acids like phenolsulfonphthalein were not. Furthermore, none of the basic compounds were absorbed except for a few like antipyrine that are so weakly basic that they are partially undissociated in an acidic solution (Figure 1).

Additional evidence that it is mainly the undissociated form of a drug which is absorbed was obtained by changing the degree of ionization of drugs by raising the pH of the stomach contents with sodium bicarbonate. Basic compounds,

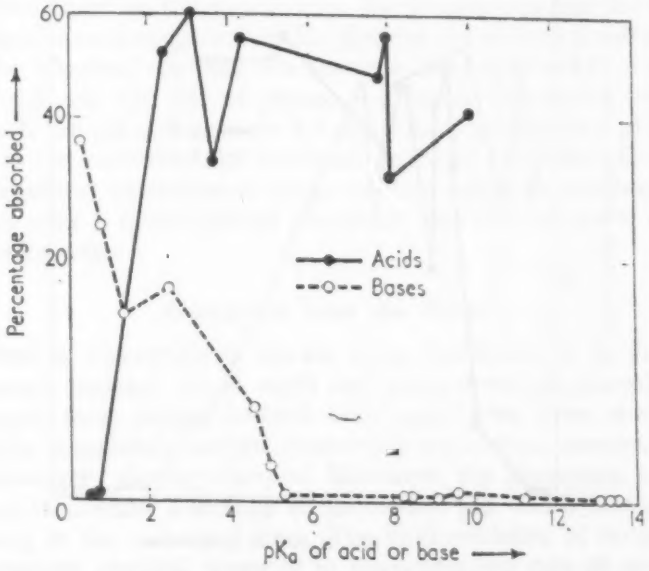

Figure 1.—Comparison between pK_a and gastric absorption of drugs in the rat.

which become more undissociated at higher pH values, were more readily absorbed from the alkaline medium. Conversely, acidic compounds, which become more ionized at higher pH values, were less readily absorbed.

Evidence that absorption occurs by simple diffusion was supplied by the observations that the amount of drug absorbed was directly proportional to the concentration within the stomach, and that one drug did not interfere with the absorption of another.

An indication that lipid-solubility is the physical property governing the passage of unionized molecules across the gastric epithelium was provided by a study of three barbiturates. These compounds were absorbed at rates roughly proportional to the lipid/water partition coefficients of their unionized forms. For example, thiopental was absorbed very rapidly, secobarbital less rapidly, and barbital relatively slowly.

The pattern of absorption from the human stomach was found to be the same as in the rat. For example, acidic drugs like salicylic acid, acetylsalicylic acid, thiopental, and secobarbital were readily absorbed; basic compounds like quinine, ephedrine, and aminopyrine were not absorbed.

Absorption from the Small Intestine

Studies of intestinal absorption have revealed that the epithelial lining of the intestine, like that of the stomach, allows the ready penetration of undissociated drug molecules and impedes the passage of ionized moieties. In experiments with rats, the entire small intestine was perfused with a drug solution, and the extent of absorption estimated from the difference in the concentration entering and leaving the intestine. A relation between the degree of ionization and the rate of absorption of drugs was revealed: the weaker acids and bases were readily

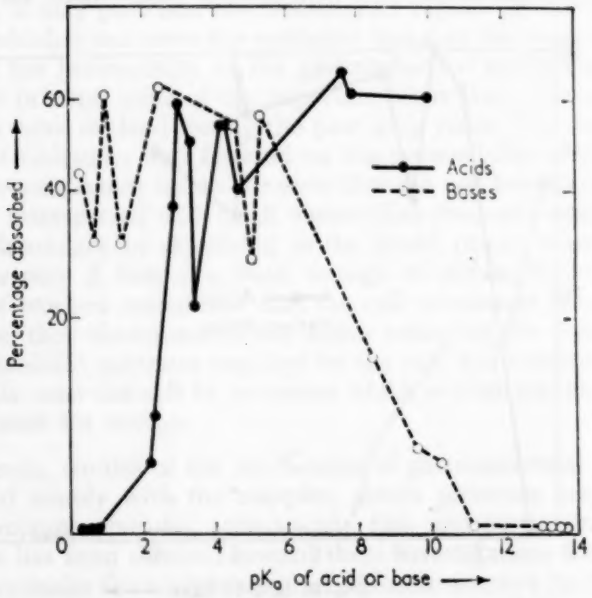

Figure 2.—Comparison between pK$_a$ and intestinal absorption of drugs in the rat.

absorbed; stronger, highly ionized acids and bases were more slowly absorbed; and the completely ionized quaternary ammonium compounds and sulfonic acids were hardly absorbed at all (Figure 2).

Additional evidence that the rate of absorption is related to the proportion of drug present as undissociated molecules was provided by experiments in which the pH of the intestinal contents was varied. For example, raising the intestinal pH increased the absorption of bases and decreased the absorption of acids; moreover, compounds which remained essentially undissociated at the various hydrogen-ion concentrations showed no change in their rate of absorption.

Since the rates of intestinal absorption of drugs were found to be dependent on the proportion of lipid-soluble, unionized drug molecules and not on the molecular weight of the compounds, it appears that the main pathway of absorption is through the lipoid areas of the intestinal boundary rather than through small aqueous channels. In support of this view, many lipid-soluble drugs of high molecular weight were absorbed more rapidly than small, lipid-insoluble molecules like urea and D_2O.

The direct proportionality between the amount of drug absorbed and the concentration of drug within the intestine suggests that absorption occurs by simple diffusion rather than by a specialized transport process. Additional evidence of the passive nature of the absorption process was seen in the failure of various drugs to alter the rates of absorption of other drugs.

Strong evidence that lipid-solubility is the physical property that determines the rate of passage of undissociated molecules across the intestinal epithelium was provided by the observation that the rates of absorption of a large number of weak acids and bases were roughly parallel to the lipid/water partition ratios of the undissociated drug forms.

Calculations based on the steady state distribution of drugs between plasma and the intestinal lumen suggest that the effective pH of the rat intestine is lower than that of the intestinal contents. For example, although the pH of the intestinal contents was 6.6, and the pH of plasma 7.4, drugs distributed between these fluids as though the pH values were 5.3 and 7.4. A zone with a pH of 5.3, possibly located at the surface of the intestinal epithelial boundary, thus appears to govern the degree of ionization of drugs as they approach the boundary to be absorbed. This view is quantitatively consistent with the pattern of drug absorption in the rat intestine.

Absorption from the Colon

The pattern of absorption in the rat colon was found to be very similar to that in the small intestine. Weak acids and bases were, in general, readily absorbed; stronger, more highly ionized acids and bases were more slowly absorbed; and the completely ionized quaternary ammonium compounds and sulfonic acids were very slowly absorbed. Moreover, the absorption of weak acids and bases was favored by a change in the colonic pH which increased the proportion of drug in the unionized form. The lipid-solubility of drugs was shown to be an important physical property in governing the rate of absorption. For example, nine barbiturates with similar degrees of ionization were absorbed at rates roughly proportional to the chloroform/water partition ratios of the unionized drug molecules (Table 1).

Absorption by Active Transport

Although the intestinal absorption of numerous drugs and other foreign organic compounds may be explained in terms of simple diffusion across a lipid-like boundary, there is evidence that a drug may also be absorbed by a specialized active transport process if its chemical structure is similar enough to that of the substrate naturally transported. For example, the foreign pyrimidines, 5-fluorouracil and 5-bromouracil, are actively transported across the intestinal epithelium by the process which transports the natural pyrimidines, uracil, and thymine. This process differs from simple diffusion in a number of ways: transport of the solute occurs against a concentration gradient, the transport mechanism becomes saturated when the concentration of the pyrimidine is raised high enough, the process shows specificity for a certain molecular structure, and one pyrimidine may depress the absorption of another by competing with it for the transport mechanism.

Other Factors Influencing the Absorption of Drugs

Although this article concerns the mechanism by which drugs in true solution pass from the gastrointestinal lumen into the bloodstream, brief mention should be made of other factors which may modify absorption. Probably the most important of these factors is the solubility of drugs in the gastric and intestinal contents. Since drugs are usually administered in solid form, the rate of solution may become the factor limiting the rate of absorption, especially with acidic drugs which generally have a low solubility in the acid gastric contents.

Physiological variables such as the rate of gastric emptying and the degree of intestinal motility may modify the rate of absorption of a drug. Foodstuffs, mucus, or other materials within the gastrointestinal tract, may interfere with absorption by adsorbing or binding a drug.

Table 1.—RAT LARGE INTESTINE. Comparison between absorption of oxybarbiturates and lipid:water partition of the unionized form of oxybarbiturates.

Oxybarbiturate	pKa	Per cent absorbed	$\frac{C_{chloroform}}{C_{0.1\ M\ HCl}}$
Barbital (Veronal)	7.9	12	0.7
Aprobarbital (Alurate)	7.9	17	4.9
Phenobarbital (Luminal)	7.4	20	4.3
Allylbarbituric acid (Sandoptal)	7.7	23	10.5
Butethal (Neonal)	7.9	24	11.7
Cyclobarbital (Phanodorn)	7.5	24	13.9
Pentobarbital (Nembutal)	8.1	30	28.0
Secobarbital (Seconal)	8.1	42	50.7
Hexethal (Ortal)	7.8	44	> 100.0

Conclusion

When drugs are administered in true solution, two physical properties of the compounds appear to determine the rate of absorption from the gastrointestinal tract: (1) the lipid/water partition coefficient of the undissociated drug form; and (2) the dissociation constant which determines the proportion of drug in this form. Thus weak organic acids and bases are readily absorbed when present as the lipid-soluble, undissociated molecule. Completely ionized compounds like sulfonic acids and quaternary ammonium compounds are absorbed with great difficulty. Undissociated substances with low lipid-solubilities like sulfaguanidine are absorbed slowly. This pattern of absorption may be explained on the assumption that the boundary between the gastrointestinal tract and the bloodstream behaves towards foreign compounds as a lipid-like membrane.

With this information, it is possible to make predictions concerning the gastrointestinal absorption of drugs on the basis of known physico-chemical properties.

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BIOLOGIC HALF-LIFE AND TISSUE CONCENTRATIONS

JOSEPH V. SWINTOSKY

My talk will be concerned primarily with some of the practical aspects of obtaining, handling, interpreting, and applying tissue concentration and biologic half-life data as these relate to problems of interest in pharmacy. It will deal with facets of the subject which are of an introductory and philosophic nature, and I hope will be of interest to you teachers and researchers in pharmacy.

In the early 50's we were faced with some unique practical problems pertaining to sustained drug action through prolongation of absorption from oral dosage forms. It was at this time that we began some intensive studies on the determination of drug biologic half-life and rates and periods of absorption, distribution, and elimination in order to do a better job of designing and evaluating dosage forms and regimens. Fortunately, much information on absorption, distribution, and elimination (ADE) kinetics, a field then neglected by most pharmaceutically-trained investigators, was already documented in accessible scientific literature. The publications of Teorell (1), Dominguez (2), Boxer (3) and co-workers, in the English language, provided the initial stimulus and direction for some of our earliest applied studies. These aforementioned researchers have provided important mathematical models and theories which have influenced and guided much of the thought and studies of contemporary investigators. There is much other valuable information published on this subject, some of which is to be found in articles whose titles do not even suggest the presence of the information; some comprehensive articles exist in foreign languages. Fortunately Nelson, a contemporary worker, has recently written a review of absorption, distribution, metabolism and excretion citing many of the important contributions to this knowledge (4). Wagner has written a recent review of drug absorption (5).

The recent reviews summarize the subject, present the status of some of the theoretical knowledge in the field, and refer to the work of Teorell, Dominguez, Boxer, Dost, Lapp, Bray and many others. These reviews also indicate the pharmaceutical and clinical applications of this knowledge, and they merit the attention of anyone considering work in one or more facets of the subject.

Measurement of Drug in Blood and Other Body Fluids

The literature of the health sciences and related fields is replete with data involving *in vivo* concentrations of drugs, and with data describing elimination of drug from the body. Some of the data are expressed in a quantitatively useful manner. In other instances, drug elimination is described as "rapid", "moderately rapid", "slow", "very slow", or in similar unprecise terminology.

This terminology often lacks precision because a clear frame of reference is absent. The quantitative kinetic approach to handling drug tissue concentration data attempts to bring mathematical accuracy and precision to this field. It attempts to obtain the data with sufficient accuracy so that the powerful tools of

kinetics can be used to gain a clearer understanding of the ADE processes involved in drug utilization and disposition by the body.

The quantitative kinetic approach demands that good analytical methods be available for measuring drug concentrations in body fluids and tissues. Good methods have become quite commonplace for a modest number of drugs, especially the chemotherapeutic agents; however, for most of the pharmacodynamic drugs, many of which have extremely small doses, methods for their measurements in body fluids are often nonspecific, not sufficiently sensitive, or nonexistent. In recent years, methods such as liquid and vapor phase chromatography and radiochemical techniques have afforded a greater opportunity for accurate quantitative measurements of minute drug concentrations. However, one needs only to embark on an ADE study with a new potent pharmacodynamic agent to discover the complications of obtaining satisfactory measurements of drug concentrations *in vivo*. Analysis for drugs in body tissues and fliuds is still in a developmental phase, and is deserving of much more attention by investigators who can bring experience and competence to this field.

In Vivo Profiles of Drug Concentrations

Much ADE data is portrayed with Cartesian coordinate graphic plots of tissue concentrations (usually blood, serum, or plasma concentrations). Curve A of Fig. 1 is illustrative of this; no attempt is made to assign a smooth curvature to the data. Curve B assumes the process to be smooth and estimates the natural curvature. Such graphs resulting from blood collections following oral administration of drugs, for example, are definitive, and they give profiles of drug concentrations versus time under the conditions employed in obtaining the data. They are valuable and over the years have been useful.

The smooth plot of Fig. 1 has the appearance of a "die-away" curve through the 2 to 8 hour interval. Extrapolating the curve to its natural intersection with the ordinate axis gives the curve of Fig. 2. If now we draw blocks for each hourly interval, which represent the real or apparent drug concentrations at 1, 2, 3, 4, etc. hours, we obtain a histogram portrayal of this curve. By measurement, one can readily establish that the height of each block is some fixed fraction of the height of the preceding block of the histogram. In this illustration the fraction is 77/100.

Equations Describing Exponential Drug Disappearance

When such a natural relationship exists, the die-away curve is defined mathematically by the expression

$$C = C_o e^{-kt}. \qquad (1)$$

where if the height of the blocks at the intersection of the curve represents blood drug concentrations

C = concentration
C_o = the hypothetical concentration at zero time determined in this instance by extrapolation
k = the net coefficient of drug elimination
e^{-k} = the ratio of the height of each block to the preceding one, which in this instance is 0.77
and t = time in appropriate units.

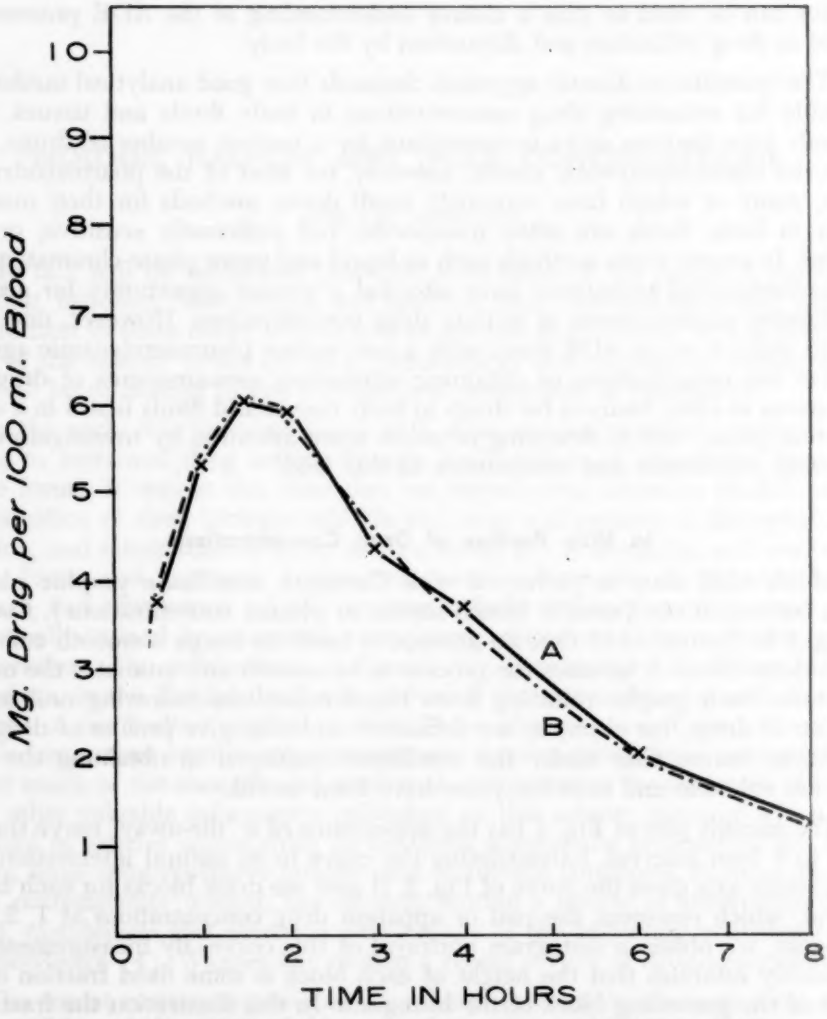

Figure 1.—Hypothetical blood concentration curve utilizing Cartesian coordinate plot. Curve A connects experimental points by straight lines. Curve B assumes drug elimination process to be smooth, and a natural curvature is estimated from the data.

For convenience. we may replace e^{-kt} with $10^{\frac{-kt}{2.303}}$ resulting in the equation

$$C = C_0 10^{\frac{-kt}{2.303}}. \qquad (2)$$

In its logarithmic form this equation is

$$\log C = -\frac{kt}{2.303} + \log C_0 \qquad (3)$$

which is the equation of a straight line in log C and t.

If we use the die-away concentration versus time data of Figs. 1 or 2 and plot them according to this equation, we obtain the plot of Fig. 3.

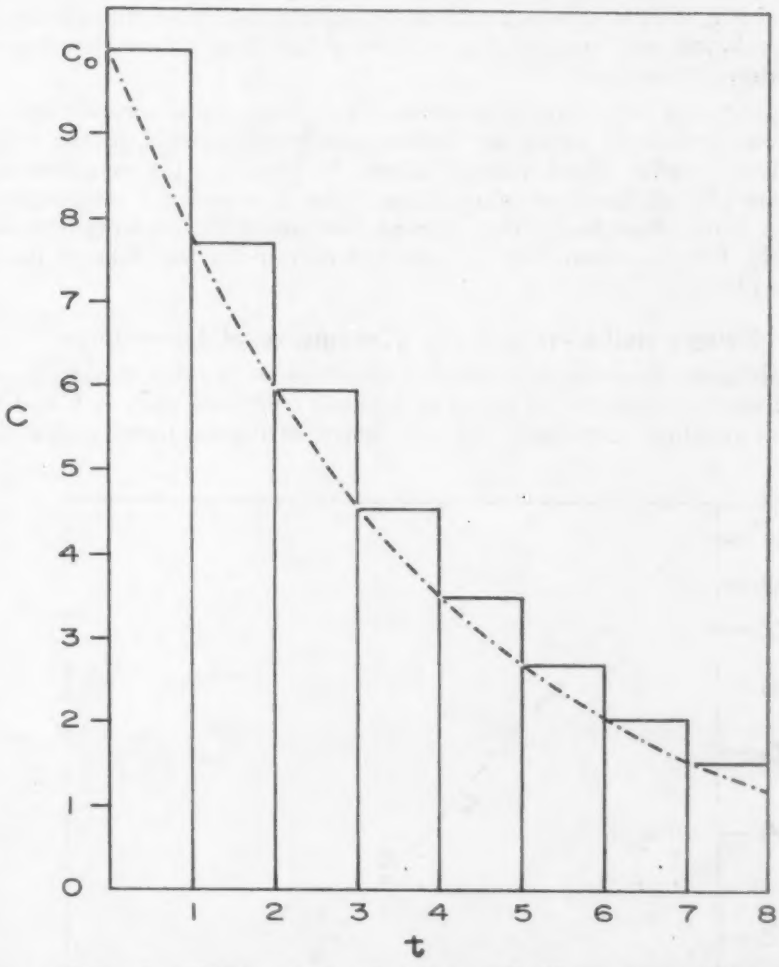

Figure 2.—Histogram portrayal of the smooth die-away curve of Figure 1 extrapolated to its natural intersection with the concentration axis. The height of each hourly block is a fixed fraction of the height of the preceding block.

We may say that the elimination process is exponential or follows first order kinetics, *i.e.*, the drug disappearance rate at any time is proportional to the concentration at that time. According to this concept, the period during which the drug falls from one concentration to one-half this concentration during an exponential process is called the biologic half-life, and is related to the net coefficient of drug elimination, k, as follows:

$$k = \frac{0.693}{t_{1/2}} \qquad \text{or } t_{1/2} = \frac{0.693.}{k} \tag{4}$$

The plot of Fig. 3 is a useful one because $t_{1/2}$ can be determined from it by inspection. In this instance $t_{1/2}$ is about 2.6 hours. Substituting this value into the preceding equation, $k = 0.27$ reciprocal hours, *i.e.*, at any instant the rate of drug disappearance is 27% per hour. The value of $\frac{-k}{2.303}$ is the slope of the straight

line plot of Fig. 3. It is apparent that the straight line plot has the advantage of easy interpolation and extrapolation whenever the drug elimination process is approximately exponential.

It appears that for a considerable number of drugs net absorption and elimination follow processes which are approximately exponential in the range of therapeutically useful blood concentrations. In practice, the semi-logarithmic straight line plot of blood or other tissue levels is seen most frequently after completion of the absorption phase. Though the data of the absorption phase can be valuable, for this discussion we will concentrate on the data of the post-absorptive phase.

Biologic Half-Lives and the Convenience of Scalar Units

The ability to describe drug blood concentrations or other tissue concentrations, and elimination rates, in terms of biologic constants such as k and $t_{1/2}$ is not only of practical importance for the design of dosage forms and regimens

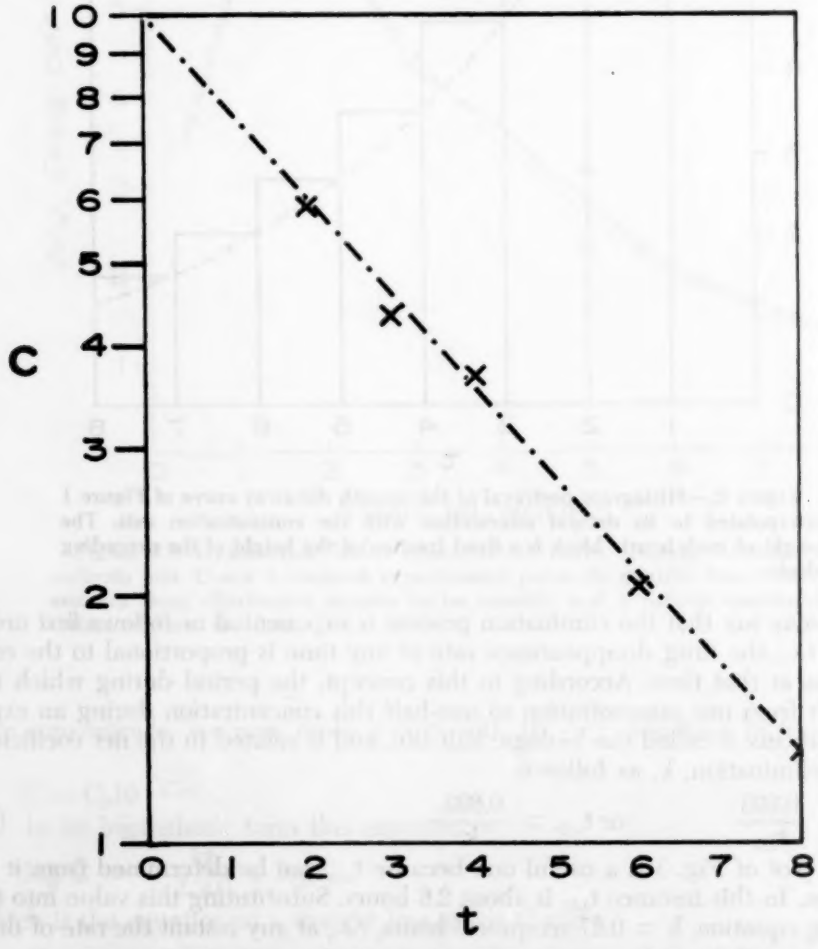

Figure 3.—A plot on semi-log scale of the die-away data of Figures 1 and 2 according to the requirements of equation 3.

and for other purposes, but is a step forward in the communication process. These constants are scalar quantities which lend themselves to comparison and tabulation. The teaching and communication process becomes simplified when one can say, for example, that the biologic half-life in humans of sulfamethylthiadiazole is two hours whereas that of sulfisoxazole is eight hours.

Table I lists the approximate biologic half-life of several compounds. It is noted that a drug such as sulfamethythiadiazole is eliminated quite rapidly, whereas for a compound such as sulfamethoxypyridazine elimination is quite slow. Within a single class of compounds, such as the chemotherapeutic sulfonamides, there is a considerable spread in the biologic half-lives. The literature also indicates that there are species differences in biologic half-lives, as illustrated for example with sulfaethidole (SETD), where the biologic half-life in cattle is between one and two hours, whereas in man it is about eight hours.

TABLE 1—THE APPROXIMATE BIOLOGIC HALF-LIFE, IN HOURS, OF SEVERAL SULFONAMIDES DETERMINED FROM BLOOD CONCENTRATION DATA

	$t_{1/2}$ in man, hours
Sulfamethylthiadiazole	2
Sulfaethidole	8
Sulfisoxazole	8
Sulfamethoxypyridazine	34

Variations in $t_{1/2}$ and k for a Single Drug

Though Table I lists single numerical values for the biologic half-life, it should be noted that these are reported from data usually restricted to a therapeutic blood concentration range, and that there may be variations in $t_{1/2}$ and k for a single subject and for different subjects. Like other biologic parameters, $t_{1/2}$ and k values for a given drug are subject to variations effected sometimes by physiologic differences in age and sex, states of health, types and quantities of food and drink, acid-base balance in the body, concomitant administration of other drugs, etc. Thus these "constants" are approximations representing mean values, as is illustrated, for example, in the data of Fig. 4. In Fig. 4 are data for the $t_{1/2}$ of SETD in human subjects receiving doses from 0.5 to 4.0 gm by the intravenous and oral routes. Our experience indicates that in the blood concentration range of about 5 to 20 mg SETD per 100 cc blood, $t_{1/2}$ is independent of route of administration; however, Fig. 4 illustrates that for these particular subjects, $t_{1/2}$ varied from about 5 to 14 hours, with most subjects giving $t_{1/2}$ values of 7 to 10 hours when single doses were administered. Also, since today the $t_{1/2}$ and k values for specific drugs are based on rather small samples of select individuals, they will be subject to some revision when more data are obtained under a variety of experimental regimens and are reported in this manner.

Averaging of Drug Concentration Data from Several Blood Profiles

Normally, in the procurement of drug concentration data from a single subject at several doses, or from a number of subjects at one or more doses, the question arises as to how to interpret the composite data in order to obtain "average" values of $t_{1/2}$ and k. Even if drug elimination rate is independent of dose size in the dosage range being studied, subjects vary from one another in their rates and efficiencies of drug absorption, and in their volumes (and

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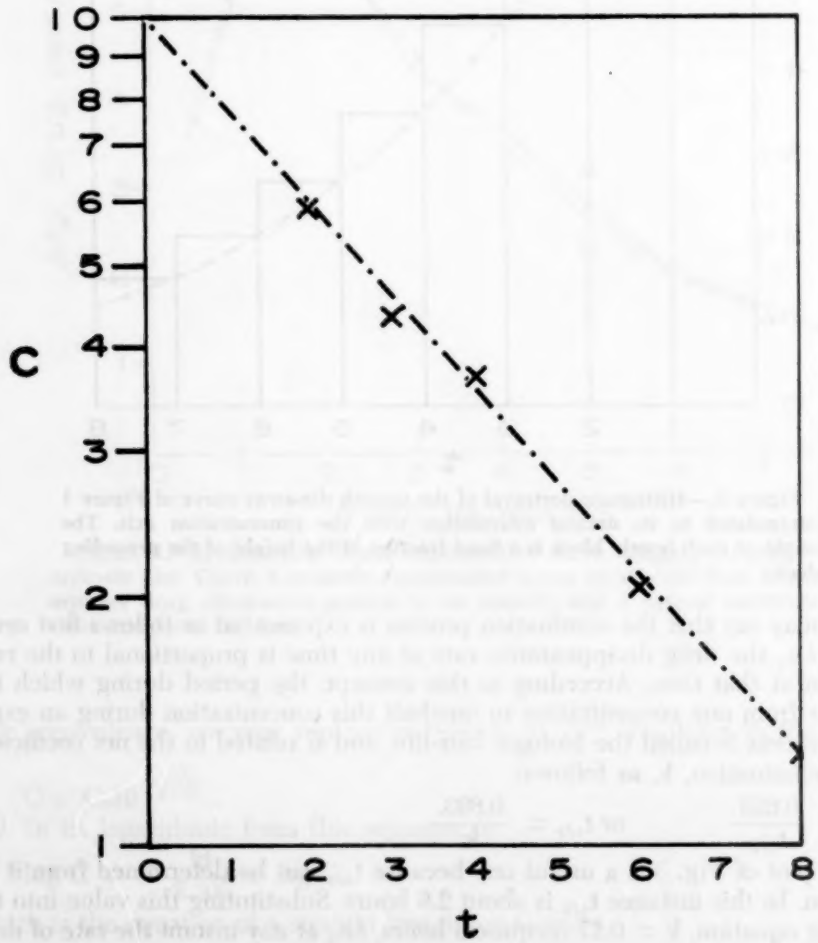

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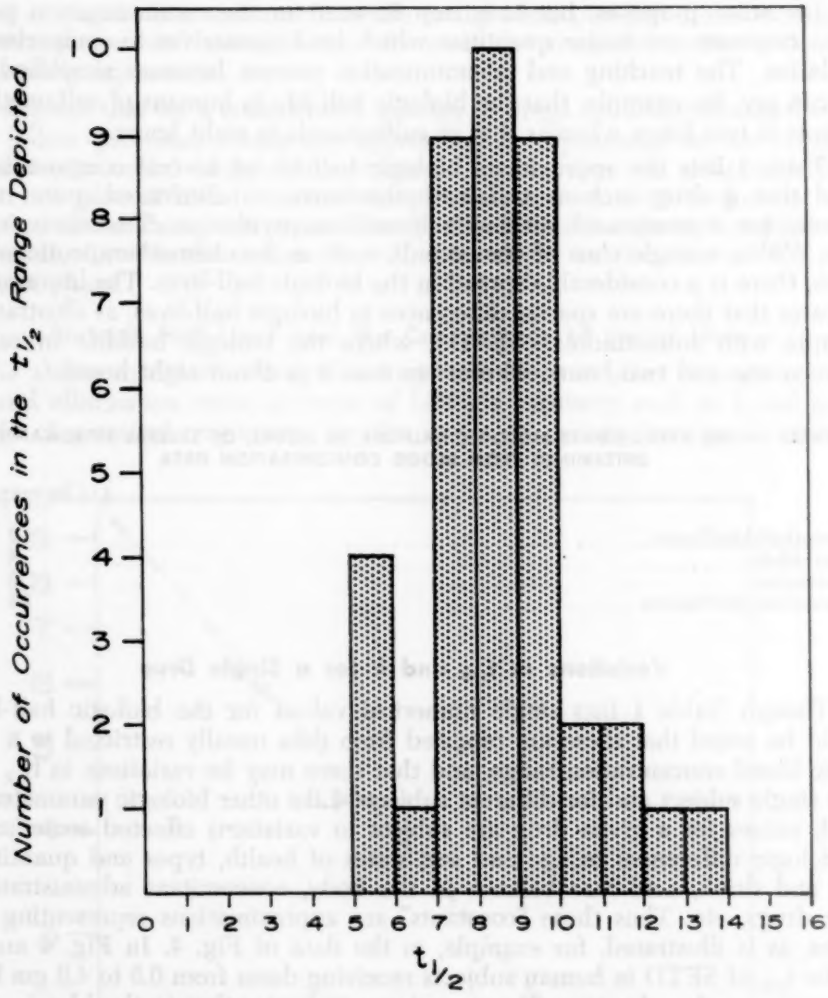

Figure 4.—Histogram of the $t_{\frac{1}{2}}$'s in hours observed from blood concentration data following oral or intravenous administration of 39 individual sulfaethidole doses, ranging from 0.5 to 4 gm, to 13 normal human adult subjects. Each bar represents $t_{\frac{1}{2}}$'s lying between one number and up to but not including the succeeding number. The peak of the distribution therefore lies at a value above 8 but less than 9, and the range is between 5 and 14 under the conditions employed in the studies.

weights), and will exhibit different blood profiles for a specific drug. Thus plots of the blood concentrations for one or more doses of a given drug will rarely be superimposable.

Figure 5 illustrates an example of plots of blood concentrations in a single subject receiving intravenous injections of 1, 1.5, and 2 gm SETD. We note that the apparent C_o's for the three doses are different, that distribution equilibrium is not complete until after 1 hour has elapsed, and that the 2- to 8-hour data approximates an exponential relationship.

To obtain the "average" $t_{1/2}$ and k for these related sets of data one might first consider the interrelationships of two related straight lines defined by

$$ay = bx + c$$
$$dy = ex + f.$$

The single line which is the average is given by

$$\frac{(a + d)y}{2} = \frac{(b + e)x}{2} + \frac{(c + f)}{2}. \quad (5)$$

Similarly with excretion data

$$\log C_1 = -\frac{k_1 t}{2.303} + \log (C_o)_1$$

$$\log C_2 = -\frac{k_2 t}{2.303} + \log (C_o)_2$$

$$\log C_n = -\frac{k_n t}{2.303} + \log (C_o)_n$$

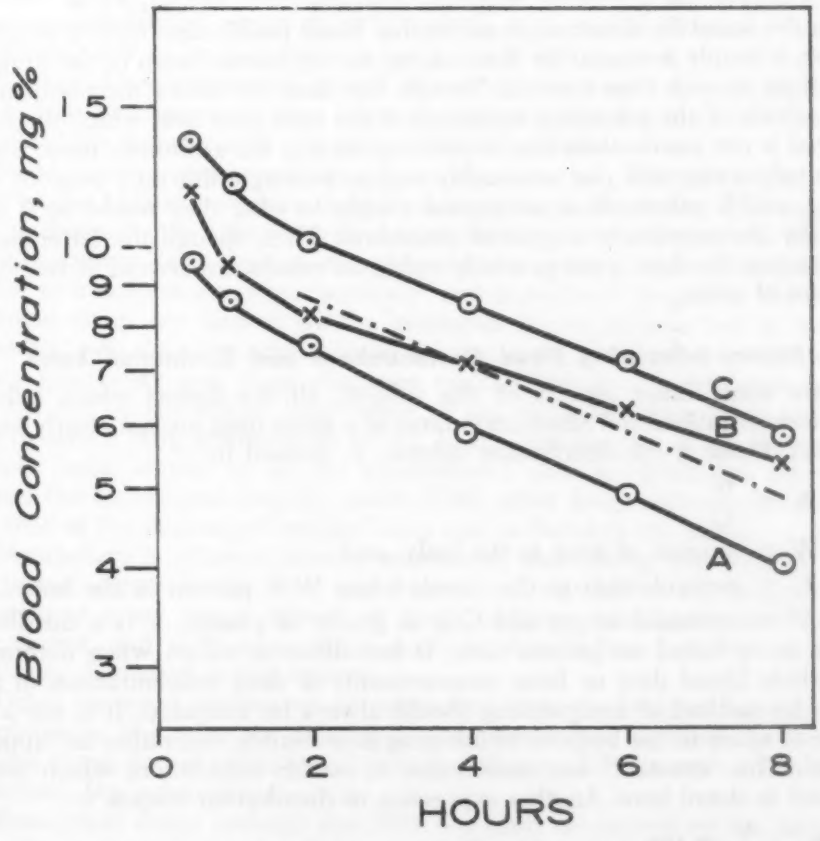

Figure 5.—Free SETD blood concentrations in an adult human subject following A) 1, B) 1.5, and C) 2 gm intravenous injections of the drug. The slope of the broken line is the "average" slope of the three solid lines between 2 and 8 hours. Data from reference 6.

The sum of the equations is

$$\log C_1 C_2 \ldots C_n = -\frac{(k_1 + k_2 + \ldots . k_n)t}{2.303} + \log ((C_o)_1 (C_o)_2 \ldots . (C_o)_n) \quad (6)$$

and the single line which summarizes the n related events described by the equations may be written

$$\frac{\log C_1 C_2 \ldots . C_n}{n} = -\frac{(k_1 + k_2 + \ldots . k_n)t}{2.303\ n} + \frac{\log (C_o)_1 (C_o)_2 \ldots . (C_o)_n}{n} \quad (7)$$

Thus to obtain a single "average" line describing the three sets of data in Fig. 5, one would sum the logs of the concentrations at each given time interval and divide each set by 3. Similar determinations at each time interval would result in the data for the "average" line.

On the other hand, if the data for each individual were plotted separately and the $t_{1/2}$ and k determined for each line, from equations 4 and 7 it is shown that the average k is an arithmetic average and the average $t_{1/2}$ a harmonic mean average, *i. e.*,

$$\frac{k_1 + k_2 + \ldots . k_n}{n} = \left(\frac{1}{(t_{1/2})_1} + \frac{1}{(t_{1/2})_2} + \ldots . \frac{1}{(t_{1/2})_n}\right)\frac{0.693}{n} \quad (8)$$

In the scientific literature, considerable blood profile data from a number of subjects is simply averaged by determining the arithmetic mean of the drug concentrations at each time interval. Though this does not follow the mathematical requirements of the preceding equations, if the time span over which the data is collected is not inordinately long relative to the $t_{1/2}$, the arithmetic mean concentration values may still plot reasonably well as a straight line on a semi-log scale. The $t_{1/2}$ and k values often correspond closely to what they would be if determined by the previously suggested procedure. Thus, though the latter method of averaging the data is not precisely right, the results are arrived at simply and often are of value.

Factors Influencing Blood Concentrations and Elimination Rates

Like many other aspects of this subject, all the factors which influence blood concentrations and elimination rates of a given drug are not clearly known. One such factor is the distribution volume, V, defined by

$$V = \frac{W}{C} \quad (9)$$

where W = amount of drug in the body, and

C = concentration in the tissues when W is present in the body...

When W is expressed in gm and C is in gm/cc of plasma, V is a distribution volume in cc based on plasma data. It has different values when determined from whole blood data or from measurements of drug concentrations in other tissues. Its method of computation should always be indicated. It is not a true volume of space in the body to which drug is accessible, but rather an "apparent volume". This "constant" has some value in certain calculations which are not discussed in detail here. Another expression of distribution volume is

$$V\% = \frac{V}{V_s} \times 100 \quad (10)$$

where V% is the per cent distribution volume, and

V_s is the total volume of the subject.

The magnitudes of V and V% are influenced by the extent of accessibility of drug to various body tissues, and also by binding sites and depots which may sequester the drug. The extent of binding or depot sequestration and the rates at which drug can be unsequestered or transported will likewise have a profound effect on its concentrations in the blood and its net rate of elimination from the body. Drug that is bound to muscle tissue, for example, tends to reduce the concentration which might be accessible to other tissues. Likewise, drug that is bound cannot be cleared by the kidney until it is released from the binding site.

A convenient expression for describing the rate of total drug elimination from the body after completion of the absorption phase is

$$\frac{dE}{dt} = kVC. \qquad (11)$$

The assumption of this equation is that V remains constant. As has been noted, through a limited body content or tissue concentration range, approximate pseudo first order kinetics are obeyed for many drugs, so that the assumption seems valid; however, it is also known that for some drugs the percentage of bound drug in a tissue is variable, and is dependent on drug concentration. Also there appear to be threshold concentrations governing the degree and extent of accessibility of certain drugs to specific tissues or body spaces. Such factors can cause V to be somewhat variable. Such variations of V, and variations in the value of k which can be caused by a number of subtle factors, are responsible in part for departures from first-order rate kinetics that are sometimes seen in plotting the log of tissue concentrations versus time.

Blood concentrations and net elimination rates are related in part to the ability of the kidney to remove drug from the general circulation. The subject of drug clearance by the kidney involves such factors as the ability of the kidney to passively excrete drug through the glomeruli, to actively secrete drug into the tubules, to transform drugs biochemically, and to reabsorb drug from the tubules.

Some drugs are filtered by the glomeruli of the kidneys but in turn are reabsorbed into the circulation via the tubules, with a low net total elimination. Kidney physiology and drug clearance via the kidney are extensive subjects that will not be considered here except to say that the kidney is an important route by which drug is eliminated (7, 8). In the case of some drugs, for example, mandelic acid, almost all of the administered dose is eliminated unchanged through the kidney and into the urine. With other drugs such as theophylline, very little of the unchanged original drug can be found in the urine.

Metabolism is often a primary mechanism for ridding the body of drugs. The tissues, especially the liver and kidney, are capable of biochemical transformation of many drugs. Almost all drugs undergo some biotransformation in body tissues, and with some drugs, such as theophylline, activity is virtually completely dissipated in this manner.

Other routes of elimination of substances from the body include the lungs via exhalation, the colon via defecation, and the skin via secretion; however, the skin and lungs do not represent important pathways for elimination except with a relatively few substances.

Since most drugs undergo loss from the body by several routes, blood and other tissue concentration measurements reflect the elimination by each route. The coefficient of elimination which is measured in an exponential plot of the data, therefore, is the sum of coefficients of the respective routes by which drug activity disappears.

Use of Tissue Concentration Data in Design of Dosage Forms and Regimens

When one can make the assumption that drug effectiveness is related to blood or other tissue concentrations, knowledge of the drug absorption and disappearance characteristics plus knowledge of permissible and effective minimal and maximal tissue concentrations can be helpful in estimating useful dosage regimens, or can be used to design dosage forms to attain the concentrations desired. This is illustrated as follows:

When SETD was studied by *in vitro* and *in vivo* methods for activity against infective organisms and for toxicity and safety, it was concluded that a very desirable range of blood levels in a dosage regimen would be 5 to 15 mg per 100 cc of blood. Following administration of 1 gm oral doses to adult human subjects, the extrapolated value of C_o was about 7 mg %. The $t_{1/2}$ and k of the drug in the blood concentration range of interest were about 8 hours and 9 %/hour (0.09 $hr.^{-1}$), respectively. About 2 hours was normally required for absorption of the oral dose. Given this information it is possible, using variations of the methods of Boxer *et al*, to calculate maximum (C_{max}) and minimum (C_{min}) blood concentrations resulting when drug is administered in consecutive fixed doses, and at fixed time intervals. For an oral dosage regimen these relationships have been expressed by

$$C_{max} = \frac{C_o r_1}{1 - r} \tag{12}$$

and $$C_{min} = \frac{C_o r}{1 - r} \tag{13}$$

where $$r_1 = 10^{\frac{-kT_1}{2.303}}$$ (T_1 is time for oral absorption) (14)

and $$r = 10^{\frac{-kT}{2.303}}$$ (T is time between doses). (15)

For SETD, when the time for oral absorption, T_1, is 2 hours, $r_1 = 0.83$. When the time for repeated administration of a 1 gm dose, T, is 6 hours, $r = 0.54$.

Substituting numerical values in the preceding equations for the condition where $T_1 = 2$ and $T = 6$ we obtain

C_{max} = 13 mg per 100 cc blood

C_{min} = 8 mg per 100 cc blood,

i.e., for subjects on which the original data for C_o, T_1, k, and $t_{1/2}$ were obtained, the administration of 1 gm of SETD every 6 hours should theoretically give a desirable range of therapeutic blood levels. When this was tested experimentally, the results illustrated in Fig. 6 checked closely with the predictions of theory. A regimen for human adults of 1 gm SETD in suspension, capsule, or other conventional oral dosage unit, therefore, is a useful one for therapeutic purposes. The results not only support theory, but also permit a fair estimate of blood concentrations that might result from different size dosage units and different dosage schedules. Also, from the absorption and elimination data one may derive clues to the dosage form designs which might result in longer maintenance of desired blood concentrations.

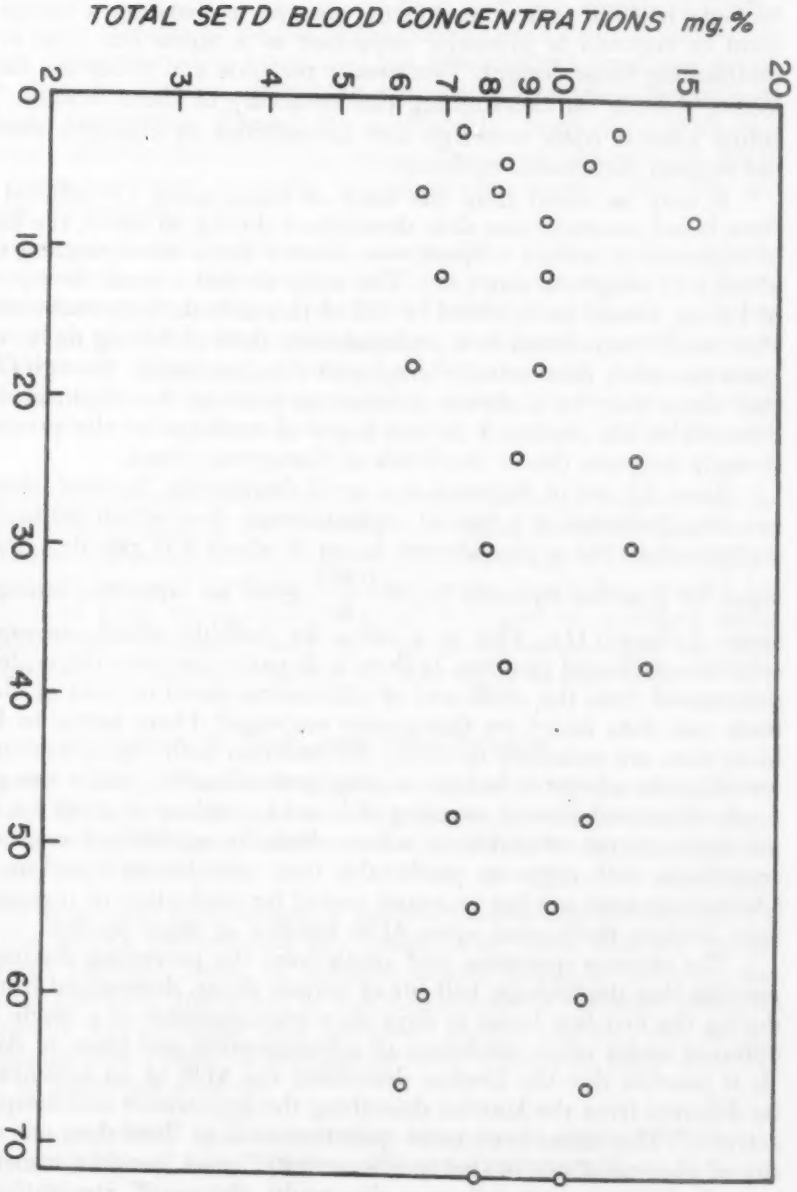

Figure 6.—Total SETD blood concentration data for 4 adult human subjects receiving 2 gm SETD followed every 6 hours by a 1 gm dose for 72 hours. Circles denote minimum and maximum concentrations observed in the 4 subjects at the times indicated. Concentrations observed conform closely to theoretical prediction of 8 to 13 mg% when $k = 0.09$ hr.$^{-1}$, $C = 7$ mg%, $T_1 = 2$ hours, and $T = 6$ hours and are substituted appropriately into equations 12 and 13. Data from reference 9.

Disappearance of Drug Activity

In what has preceded, the usefulness of the biologic half-life concept has been illustrated; however, it is well to bear in mind that dosage forms and dosage regimens must be designed to perform useful and efficient therapy. The use of biologic half-life and other kinetic data for calculating a design for a dosage form or regimen is primarily important as it steers one who is charged with establishing these designs. Therapeutic response and utility are the ultimate subjective criteria for determining the suitability of these designs. The results of actual clinical trials outweigh any assumptions or objective results that might not support the clinical evidence.

It may be noted from the work of Okita using C^{14} labeled digitoxin that from blood concentration data determined during 96 hours, the biologic half-life of digitoxin in human subjects was about 2 days, corresponding to a k value of about 0.33 reciprocal day (10). This suggests that a usual therapeutic adult dose of 1.2 mg should be followed by 33% of this dose daily to maintain digitalization. This would correspond to a replenishment dose of 0.4 mg daily, which is 2 to 4 times the adult dose actually employed therapeutically. Though Okita suggested that there may be a slower elimination constant for digitoxin which was not detected in his studies, I do not know of evidence at the present time which strongly supports this at the levels of therapeutic doses.

Since 1.2 mg of digitoxin is a usual therapeutic "loading" dose and 0.15 mg per day thereafter is a typical replenishment dose which maintains satisfactory digitalization, the replenishment factor is about 13% per day. Substituting this value for k in the equation $t_{1/2} = \frac{0.693}{k}$ gives an "apparent biologic half-life" of about 5 days (11). This is a value for half-life which corresponds to well-established clinical practice. Is there a disparity between the replenishment dose determined from the coefficient of elimination based on data of blood concentrations and data based on therapeutic response? There seems to be a disparity. More data are necessary to clarify the situation with regard to digitoxin. Caution would seem advisable before making generalizations about the pharmaceutical applications and clinical meaning of k and $t_{1/2}$ values of drugs for which clinical-use data are not available or where clinically established regimens are not in accordance with regimens predictable from calculations based on ADE kinetics. Clinical-use tests are the accepted sequel for evaluation of regimens and dosage form designs predicated upon ADE kinetics or other studies.

The obvious questions that result from the preceding discussion are: "Is it possible that the biologic half-life of certain drugs, determined from data derived during the first few hours or days after administration of a single dose, could be different under other conditions of administration and times of data collection?" "Is it possible that the kinetics describing the ADE of an administered drug can be different from the kinetics describing the appearance and disappearance of its activity?" This raises even more questions such as "how does one measure intensity of pharmacologic or therapeutic activity?", and "would the method employed in such measurements influence the results obtained?" Straightforward answers are not possible until more data are available.

For chemotherapeutic drugs, these questions probably are mainly of academic interest, because the drugs are normally highly specific, and therapeutic actions usually seem to correlate with blood concentrations. For pharmacodynamic drugs, a circumstance can be suggested which bears on the practical

application of biologic half-life data in designing and evaluating dosage forms and regimens. With some drugs, biotransformation results in the formation of new chemical entities in the body which have therapeutic actions of their own. These biotransformed agents may have distribution and elimination characteristics different from the originally administered drug and may contribute appreciably to the apparent therapeutic profile of the administered drug. If and when this circumstance exists, the ADE kinetics of the administered drug may be of less importance than the kinetics, describing the intensity of pharmacologic or therapeutic activity versus time. Though the experimental study of such kinetics is appreciably more difficult than following concentrations of administered drugs in the tissues, sparse published examples of such studies suggest that they are possible and may be valuable (12).

A conservative point of view generally accepts the validity of the biologic half-life values, as they are normally obtained and reported in the literature, based on concentrations in body fluids and tissues, for the purpose of calculating and evaluating design of dosage forms and regimens of chemotherapeutic agents. With pharmacodynamic drugs, a knowledge of the metabolic transformation products and their pharmacologic actions would be helpful in deciding whether the ADE kinetics of the administered drug give the constants desired for this purpose.

If progress is made in measuring intensity of pharmacologic response versus time and these kinetic profiles of drugs differ from those based on tissue concentrations of the administered drug, problems of terminology will arise. Terms such as biologic half-life and coefficient of elimination might be retained for constants determined from tissue concentrations, but new or qualified terms might be advisable for constants based on pharmacodynamic data; however, these conjectures await a further unfolding of knowledge in this field.

Evaluation of Drugs and Drug Products

Tissue concentration profiles for illustrating the possible merit of drugs have been used widely. In some instances conclusions drawn from these profiles have been valid, but in some instances where ancillary information is not available, the data are quite inconclusive.

Some of the most valid applications of tissue concentration profile data are *in comparing the relative performance of a single drug* when it exists, for example, in different physical forms, in different dosage forms, in different size doses, in different products, and when it is administered via different routes or dosage regimens. In well designed and controlled studies one can use, for example, blood profile data (often in conjunction with urinary or other data) to obtain answers to questions such as:

1. What is the variability in the absorption rate seen in single subjects, and between subjects, when other variables are minimized?
2. What are the effects of adjuvants, age, sex, certain diseases, or certain physiologic abnormalities on drug absorption and elimination?
3. What is the effect of dose size on absorption and elimination rates?
4. What is the effect of particle size and specific surface area on absorption of solid medication?

5. What is the effect of tablet disintegration time on rates and efficiencies of absorption, and on the excretion profile?
6. What are the relative differences in performance of two competitive products?
7. How do different routes of administration influence the rates and efficiencies of absorption of a drug, etc.?

For such evaluations relative or absolute comparisons of coefficients of absorption, periods of absorption, coefficients of elimination, and areas under the curves of Cartesian coordinate graphic plots of blood concentrations are often very useful, because variables are kept to a minimum.

It is quite another matter, however, to compare and evaluate blood profiles of drugs which are closely related chemically and therapeutically. The penicillins, chemotherapeutic sulfonamides, and tetracyclines are examples of such drugs.

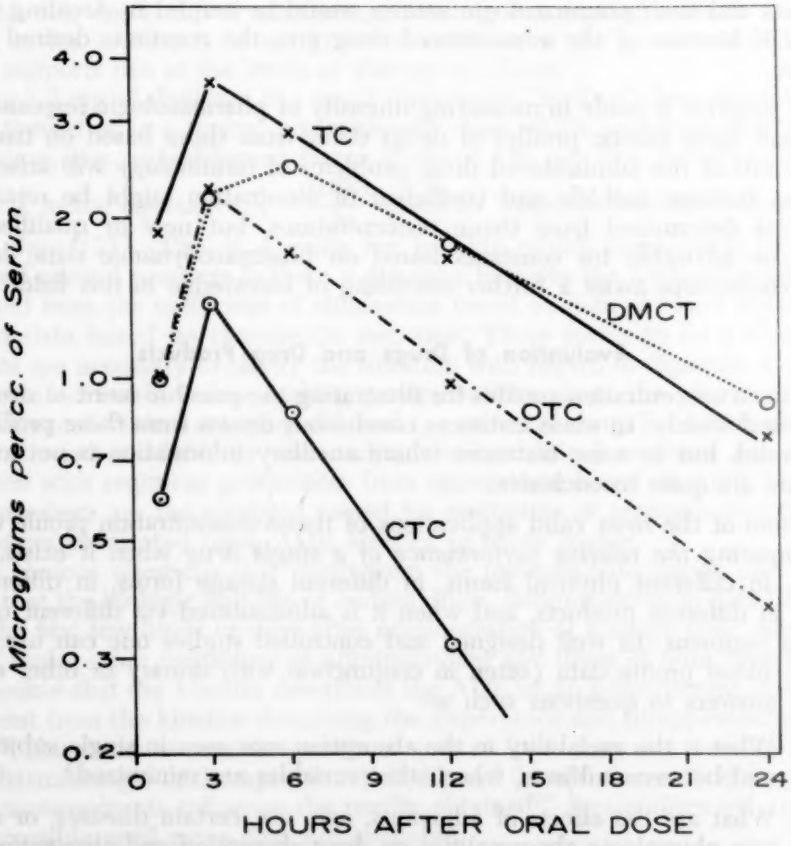

Figure 7.—Mean concentrations of four tetracycline antibiotics, e.g. tetracycline (TC), chlortetracycline (CTC), oxytetracycline (OTC), and demethylchlortetracycline (DMCT) in serum of normal young men after single oral doses of 500 mg equivalents of their hydrochlorides. The figure is plotted from data of reference 11

Data for several tetracyclines are illustrative of this situation. Figure 7 illustrates the mean concentrations of these antibiotics in the serum of normal young adults when single oral doses of approximately equivalent molar quantities of the hydrochloride salts were administered to each subject. The following inferences and comments may be made from inspection of the figure.

1. Periods and rates of absorption appear to be quite similar for chlortetracycline (CTC), oxytetracycline (OTC), and tetracycline (TC). This is suggested by the attainment of peak blood concentrations at about the same times, with exponential disappearance of drug from the body beginning on or before the third hour after drug administration. The period of demethylchlortetracycline (DMCT) absorption is longest.
2. Disappearance of these drugs from the blood follows an approximate exponential course after absorption is complete. These limited data indicate biologic half-lives of 8–9 hours for TC and OTC, 4.5–5 hours for CTC, and 12 hours for DMCT.
3. Apparent distribution volumes cannot be ascertained from these data, though TC, for example, appears to have a smaller distribution volume than OTC, thus accounting for the considerably higher serum levels of TC.
4. Peak serum concentrations are in the order TC>DMCT>OTC>CTC.
5. In the absence of other supporting data, the blood concentrations of equivalent doses of therapeutically useful drugs which are closely related chemically represent only a narrow performance profile. No conclusions can be derived from these data regarding their relative clinical utilities.
6. No conclusions are possible from these data alone regarding mechanism of elimination of drug from the body or of any possible depot or binding effects.

Kunin and Finland have discussed the difficulties of establishing clinical use-preferences of closely related drugs, and have indicated how irrelevant blood concentrations, alone, sometimes may be (13). The four drugs of Fig. 7 possess virtually identical antimicrobial spectra but they differ in their relative degrees of activity against individual bacterial species. In general, DMCT appears to be the most active on a weight or molar basis against many pathogenic bacteria. This intensity of activity factor plus others such as accessibility to various tissues of the body, relative toxicity and safety, relative incidence of undesired responses, duration of therapeutic action, and even factors unrelated to pharmacologic or therapeutic action constitute criteria for determining advantages and disadvantages and ultimate clinical use-preferences. Though one congener may give higher blood concentrations than another, the relevance of this must be considered in light of the complete pharmaceutic and therapeutic profile. Objective data such as the blood concentration profiles must ultimately be interpreted in the light of data from subjective use-tests where drug efficacy is established with individuals requiring therapy. Care must therefore be exercised as to the significance which is assigned to such objective data, so that the true clinical value of a drug is not misrepresented.

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THE PRINCIPLES GOVERNING THE PREPARATION OF SUSTAINED ACTION MEDICATION

STUART ERIKSEN

The previous authors have been concerned with detailed descriptions of the mechanics of the absorption process, and in the mathematical relationship between this process and those affecting a drug after absorption. The tacit assumption has been made that, once administered, the only processes affecting the response action obtained were physiologic. It is my purpose to bridge the gap between these physiologic ideas and the formulative ones, and to indicate how, given a drug possessing specific constants describing its absorption, distribution, and excretion, one may vary its manner of presentation to the body so that its action is prolonged.

At this point it may be well to consider some terminology. Ambiguity has resulted in the literature as to whether the absorption, distribution, and excretion (ADE) constants mentioned above (that is, absorption rate, half-life, distribution volume) are related to the active species of the drug, or to the particular molecule administered. There is merit in referring these constants only to the active moeity because one would then expect the relationships between tissue level and activity to be more significant. In this case, all chemical and pharmaceutical modifications on the drug may be considered "formulation", and the drug will have the same ADE constants in all modifications. The difficulty in obtaining this type of data (reduced to the active species) lends support to the point of view of referring these constants to the particular molecule administered, so that each chemical modification requires new ADE constants; but pharmaceutical modifications are "formulation", however, and do not alter the specific constants, but simply vary the "apparent constants", much as concentration varies a kinetic reaction rate. It is from this latter point of view that I shall discuss my topic.

In the first Figure, I have indicated the main pathways connecting ingestion and excretion of a dose of drug with particular intention of showing the potential rate determining steps in this process. These will be the potential points of attack for preparing formulations having sustained action. At the right in the figure, I have indicated the approximate position in the pathway where each dosage form enters, while the rate controlled processes are enclosed in boxes.

Any formulation which slows one or more of the rate processes indicated will result in sustained action, although some approaches are more useful than others. The two transfer processes are largely unalterable. Only disintegration and dissolution of the remaining processes can be *directly* affected by formulation. There have been many suggestions that co-administration of other chemical molecules may affect absorption, storage, deactivation, and excretion, but these have been most effective in altering absorption rates (sorbitol and B_{12}, glucosamine and tetracycline), and slowing this process can only produce sustained action when maintenance at the site of absorption is also achieved, such as epinephrine's used with injectables.

All of the process, from dissolution in the gut through excretion, can be altered through chemical modification but, as mentioned initially, these will be considered as different drugs.

Of the formulation methods presently being used to achieve sustained action, nearly all are oral preparations and utilize the principle of delayed availability to obtain a prolonged action. The first formulative sustained action product was probably Novocaine and epinephrine injection which operates strictly by depot maintenance. In 1952, the present wave of sustained action products was begun when a product using pellet-filled capsules was marketed. This product achieves

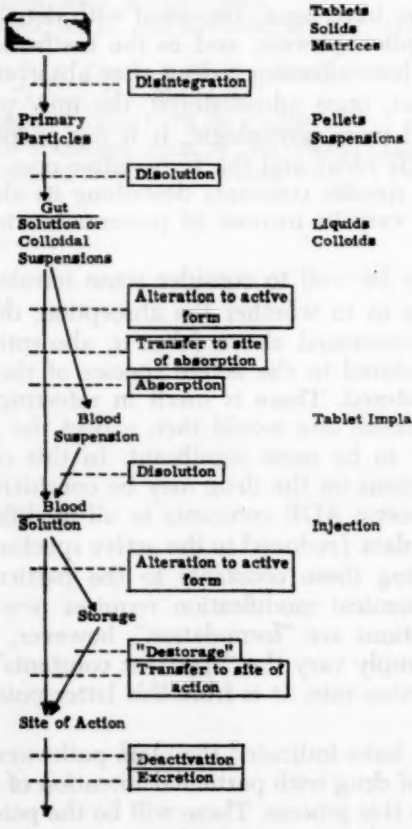

Figure 1.

sustained action by the slow release of drug from coated, drug containing pellets. Figure 2 indicates how these first products were made. The drug coated pellets may also be made by granulation as shown in Figure 3. The sustained-action portion of the pellets may be (and have been) coated with a variety of film-formers, cellulosics, fats, waxes, polymers, fatty alcohols, shellac, etc. The required per cent of coating varies from less than one to twenty to twenty-five per cent depending on the coating material, the drug, and the degree of sustained action required.

Exactly what process is responsible for release of drug from coated pellets of this type is at present unknown, but it undoubtedly varies depending on the drug (particularly its solubility) and the coating used. Studies with drugs which

precipitate on release show that weak spots or pores must exist, through which these drugs diffuse or leak. Other, more soluble dosage drugs still maintain their sustained action even when the drug inside is in water solution in the intact coating. Undoubtedly, both methods are at work.

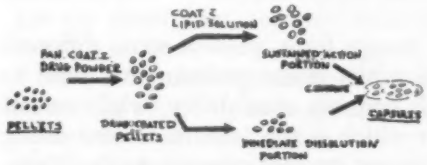

Figure 2.—Preparation of Sustained Action Pellets.

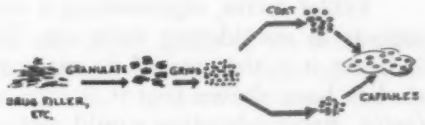

Figure 3.—Preparation of Sustained Release Granules.

The different colors present on pellets in capsules have led to misconceptions about "timed release" of these forms. Although some uncoated pellets are present, the remaining pellets are not "timed" to release at any set interval. All pellets are essentially the same, with perhaps two or three groups representing levels of coating. The sustained release phenomenon is obtained through the statistical distributions within the groups of coating imperfections, pores, thin spots, etc. Thus, it is not surprising that time-per cent released plots on arithmetic or logarithmic-probability paper yield relatively straight lines.

Sustained action materials in powdered form have been prepared, generally using two methods: resin bound and complexed drug. Resin bound drugs are prepared using standard ion-exchange techniques and acid (carboxyllic or sulfonillic) or basic (amine) resins. Release from ion exchange resins is largely a mass-action phenomenon, with hydrogen ion in the equation. The rapidity with which this type of equilibrium takes place *in-vitro* suggests that only lack of available water or slowed diffusion out of the solid pellet could result in any sustained action in-vivo, and studies on amphetamine and creatinine resinates seem to support this view.

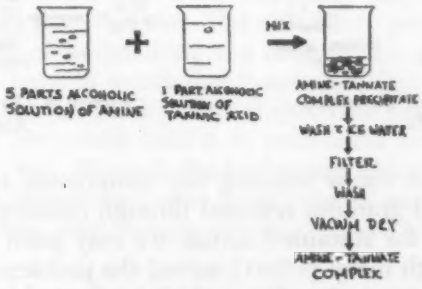

Figure 4.—Preparation of Amine-Tannate Complex.

Complexed drug forms are prepared by precipitation as shown in Figure 4. Release from these substances is controlled by solubility-dissociation as well as pH and available water. Amphetamine tannates have achieved some success in this class.

Tableted sustained action dosages have all utilized a matrix of insoluble or slowly-digestible material, usually a wax, to control availability. The next two

figures (Figures 5 and 6) indicate the methods of preparation currently in use. Prolonged action of these forms is achieved by control of the available surface for solution, through masking the drug in a porous or digestible matrix. Initial priming drug is handled by the external coating of the tablet, or by the natural occurrence of free drug at the surface of the matrix, in opposition to pellet forms where it is simply added to the capsule contents.

Tablet forms, representing a single unit dosage form, present some different aspects in considering their use. The official tablet disintegration tests tend to indicate it is the rate of disintegration which controls availability, while recent studies have shown that it is rate of solution which is the important controlling factor. Reconsideration would certainly change our present concern in the literature about setting up a "maximum disintegration time for tablets for complete availability".

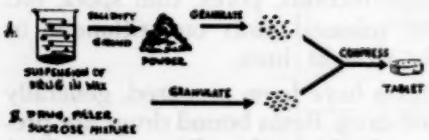

Figure 5.—Sustained Release Tablets.

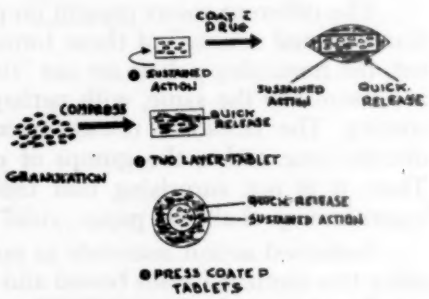

Figure 6.—Sustained Release Tablets.

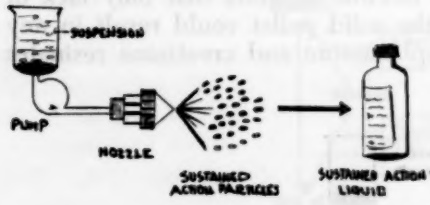

Figure 7.—Preparation of Sustained Action Liquids.

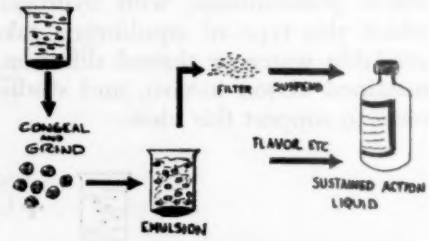

Figure 8.—Preparation of Sustained Action Liquid.

In defense of those forms utilizing the compressed tablet as a vehicle for ingesting the individual granules released through disintegration, and which are *themselves* responsible for sustained action, we may point out that they have in this way (action through many pellets) solved the problem of stomach emptying time and its effect on release. Any form which is affected by the pH of its release medium will be affected by emptying time, and the simplest way to "even out" these differences is to force the stomach to empty hundreds of small particles, each at a different time.

The present sustained action products which are liquids, are all suspensions of drug-matrix particles, though the methods of preparation differ. (Figures 7 and 8). Thus they are controlled in much the same way as tablets.

We can categorize all the above into three groups: those achieving delayed availability through coating, matrix, or chemical interaction (resin or complex).

All of these methods of formulation are at the mercy of available water, pH, digestive processes (particularly attrition) and stomach emptying time. Some concern has been voiced about the effect of site of gut absorption and whether selective sites are available. Recent work, on penicillin, has suggested that while massive oral doses of drug do not increase the amount of drug available to the gut for absorption, selected sites of absorption do not seem to be the complete answer.

In a concluding statement, some mention should be made of the controlling factors in selecting a drug for sustained action formulation, and there should be some consideration of rate determining steps in the ingestion-excretion process which are not presently being used.

The required dose and blood level of a drug must influence its selection for sustained action formulation. If it is too large, when up to 25% sustained action coating is added, the three or more doses required could represent a formidable quantity to the patient.

The toxic/effective dose ratio is also of concern because of the possibility of the patient receiving all the doses at once due to error or intestinal contents. One case in my own experience is that of a man who took an amphetamine sustained action capsule containing wax-coated pellets and washed it down with a shot of whisky, he then proceeded to walk the walls for four hours.

Finally, the ADE constants of the drug must be considered. A sustained action digitoxin for instance, with its very long action in the normal state, would be gilding the lily.

Considering other potential sites for creating rate-determining steps in the injection-excretion pattern, the possibility of the discovery of new additives to increase or control the rates of absorption, maintainance at the action site, or detoxification and excretion, must be considered, but these will be major pharmacological discoveries; let us consider formulative ones.

Any attempts at effects in altering rates of absorption in the gut must be accompanied by some artifice to maintain the dosage form in the gut while it works; perhaps it would be possible to 'string' the patient with a plastic fishline with a sinker on it, or even a fish hook. This latter might best be suggested for suppository sustained action formulas. The skin offers perhaps the best area. The large surface, the ease of maintaining the drug at the absorption site, and the pleasure some people have in bandaging themselves (my children, for example) would seem to make this an ideal potential site. One needn't consider only ointments and bandages; you could hold it in your hand or stick it in your ear. In any event we can say that, although the best means of achieving sustained action has still probably not been found after nine years of experience, the indications are that like death, taxes, and foreign aid they're here to stay.

DIFFUSION IN OINTMENT BASES

W. I. HIGUCHI

While diffusional behavior in the ointment, *per se,* is often not the most important factor in ointment design there are situations in which an understanding of the problem is essential to the pharmacist. These are, for example, instances in which drug is relatively rapidly absorbed and some release control measures within the vehicle are desired. In another application, the design of protective ointments, the transport rate of the noxious agent in the ointment phase is clearly most important.

Recent investigations, both experimental and theoretical, have led to a much better understanding of factors influencing transport of materials into and through ointment bases (1–4). In a number of instances, particularly in the limiting cases, our understanding of some of the relationships is quantitative. In other situations, theory is of qualitative or of semi-quantitative value, but clearly useful as a guide to good formulations.

The purpose of this report is to review the theory and its application and to point out the important factors, some of which are sometimes overlooked when the behavior of ointments is presupposed from intuition only. It is hoped that, while this presentation is perhaps not suitable for direct consumption by all students at the undergraduate level, it should be helpful to the instructors in discussing the subject of ointments. While there are many aspects of ointment behavior in which the phenomenon of diffusion is important, we shall restrict our discussion to a special case of drug release from ointments.

General Considerations. Let us define the problem by referring to Figure 1 where the situation is illustrated. Suppose a layer of ointment is applied to a receptor surface, the skin for example. Then how and to what extent will the diffusional behavior of drug in the ointment base influence the amount and the rate of release of the drug from the ointment? It is clear that to give a general answer to this question we must understand the transport processes of the drug both in the receptor phase as well as in the ointment base since these are consecutive processes. If the skin is impermeable to the drug, even the "best" formulations will be of no value. The more permeable the receptor, the greater will be the opportunity for varying the release rate by altering the diffusional behavior of the drug in the base. In the present analysis, we shall consider only those cases in which the receptor phase may be considered to be a perfect absorber*, *i.e.*, "free" release from the ointment with the rate being controlled entirely by the diffusional resistance of the ointment base. Therefore, this discussion pertains mainly to situations in which the pure drug, or the drug in conventional formulations, possesses a relatively high rate of receptor penetration. One might argue,

* As discussed by T. Higuchi (reference 3), when the release rate is controlled primarily by the permeation resistance in the receptor phase (which is probably the usual case for intact skin), then the drug diffusion rate in the ointment phase becomes unimportant. In this case what is important, however, is the thermodynamic activity of the drug in the essentially concentration-gradient-free ointment base, the driving force for skin penetration being the thermodynamic activity. In these cases controlled release may be obtained by controlling the thermodynamic activity of the drug in the vehicle.

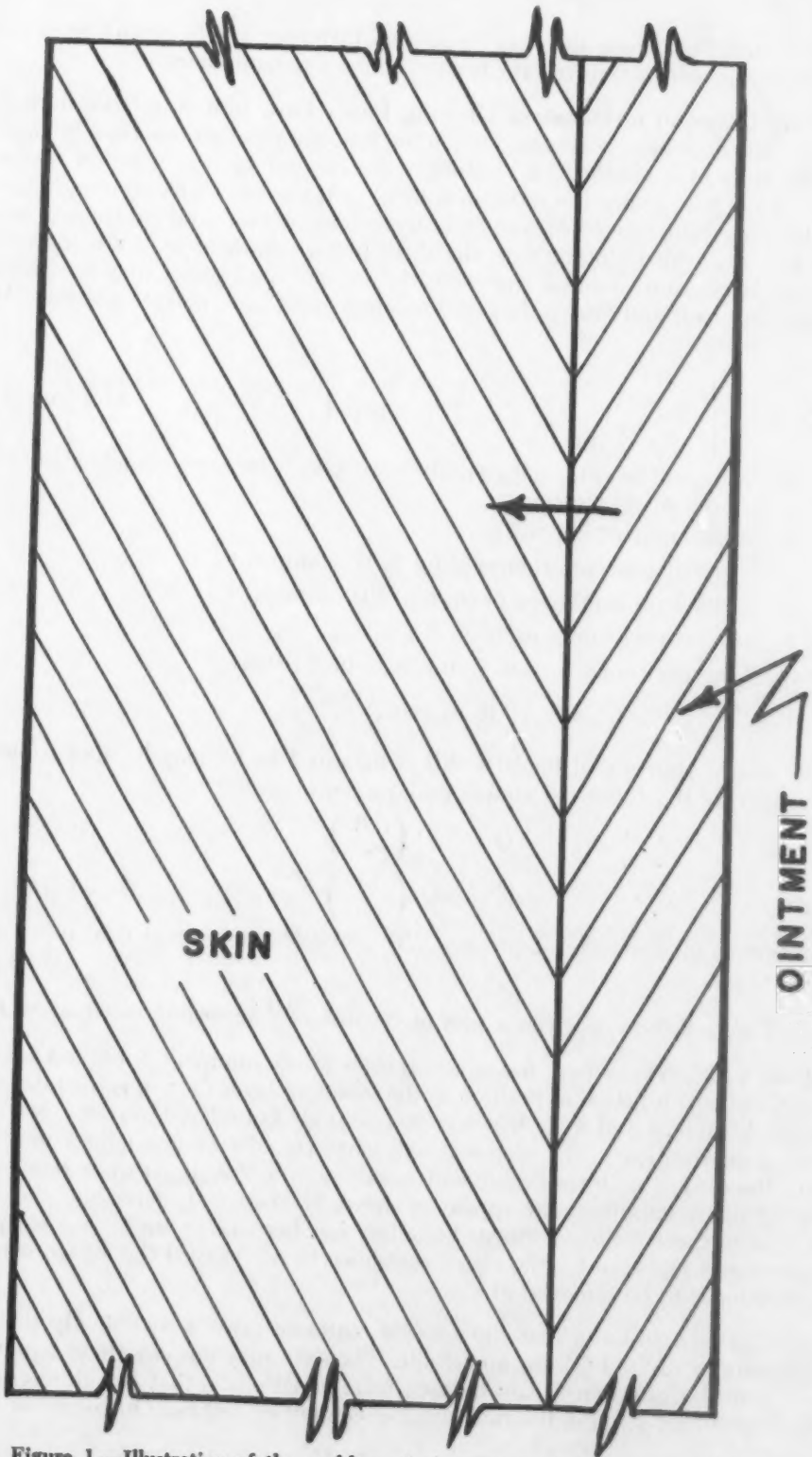

Figure 1.—Illustration of the problem of ointment applied to receptor (skin).

and he would be correct, that this discussion, therefore, really applies to *in vitro* experiments in which free release from ointments is maintained.

Drug Diffusion in Ointment Obeying Fick's Law. Simple relationships describing diffusion may be obtained when the following assumptions can be made: (a) the drug in the vehicle is uniformly distributed in true solution obeying Henry's Law (*i.e.*, either the solution is ideal or the solute concentration is low), (b) the drug diffusion coefficient is independent of time and position in ointment, (c) components other than the drug in the ointment may not leave the ointment phase, and material from outside the ointment phase may not diffuse into the ointment, and finally, (d), the receptor must be a perfect absorber. We may then write (3)

$$Q = hc_o\left[1 - \frac{8}{\pi^2}\sum_{m=o}^{\infty}\frac{1}{(2m+1)^2}\exp\left(\frac{-D(2m+1)^2\pi^2 t)}{4h^2}\right)\right] \quad \text{eq. (1)}$$

Q = amount of drug released at the receptor-ointment boundary per unit area of application.
h = thickness of applied layer.
c_o = initial concentration of drug in the ointment
D = diffusion coefficient of drug in the ointment
t = time after application.

In terms of the per cent released, R, this may be written

$$R = 100\frac{Q}{hc_o} \quad \text{eq. (2)}$$

It can be shown that for $R \cong 30\%$ equations 1 and 2 may be approximated rather well by the following simplified equations.

$$Q = 2c_o\left(\frac{Dt}{\pi}\right)^{1/2} \quad \text{eq. (3)}$$

$$R = 200\left(\frac{Dt}{\pi h^2}\right)^{1/2} \quad \text{eq. (4)}$$

For purposes of discussion, equations (3) and (4) are a great deal more convenient to use.

In Figure 2 there is given a plot of R versus $\frac{Dt}{h^2}$ according to equation (2). By going to Figure 3 where the concentration in the ointment is plotted for different times as a function of position in the ointment layer ($x = o$ is the ointment-receptor boundary and $x = h$ is the ointment-air boundary) we may see how the drug distribution in the ointment will vary. Initially ($t = o$) the concentration of the drug is uniform throughout from $x = o$ to $x = h$. At some time after, however, the distribution may appear as shown by the $t = t_1$ curve, *i.e.*, the drug very near to the receptor-ointment boundary has been taken up by the receptor. At later times (t_2, t_3 to t_4) the curve continues to fall toward the x-axis as more drug continues to be removed at $x = o$.

Let us now suppose that the applied ointment layer is sufficiently thick so that equations (3) and (4) are applicable. Then we may employ these equations to evaluate the situation. It can be seen from equation (3) that two things are at one's disposal for varying the rate and the amount of release. One of these is c_o,

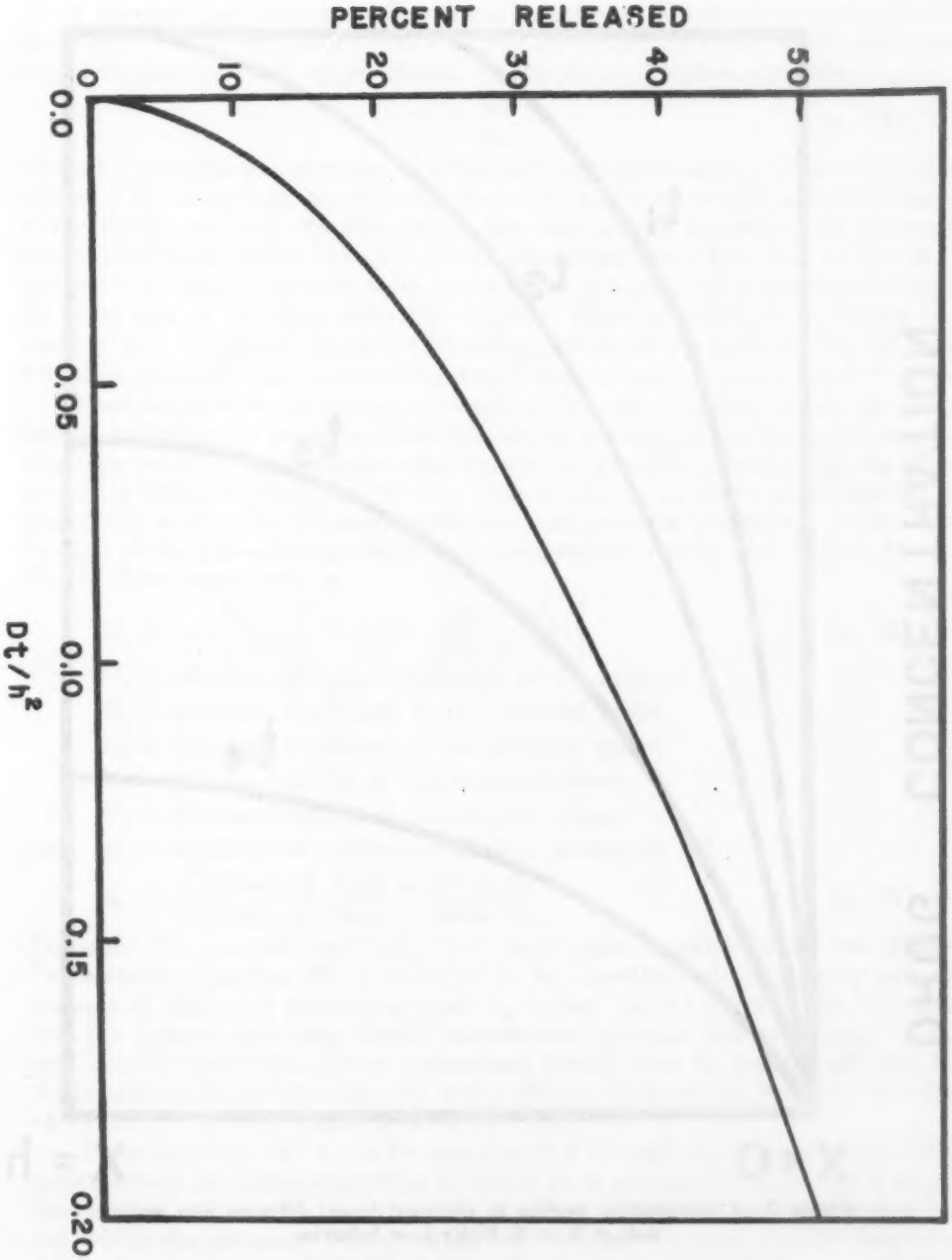

Figure 2.—Plot of equation 2, per cent release versus time.

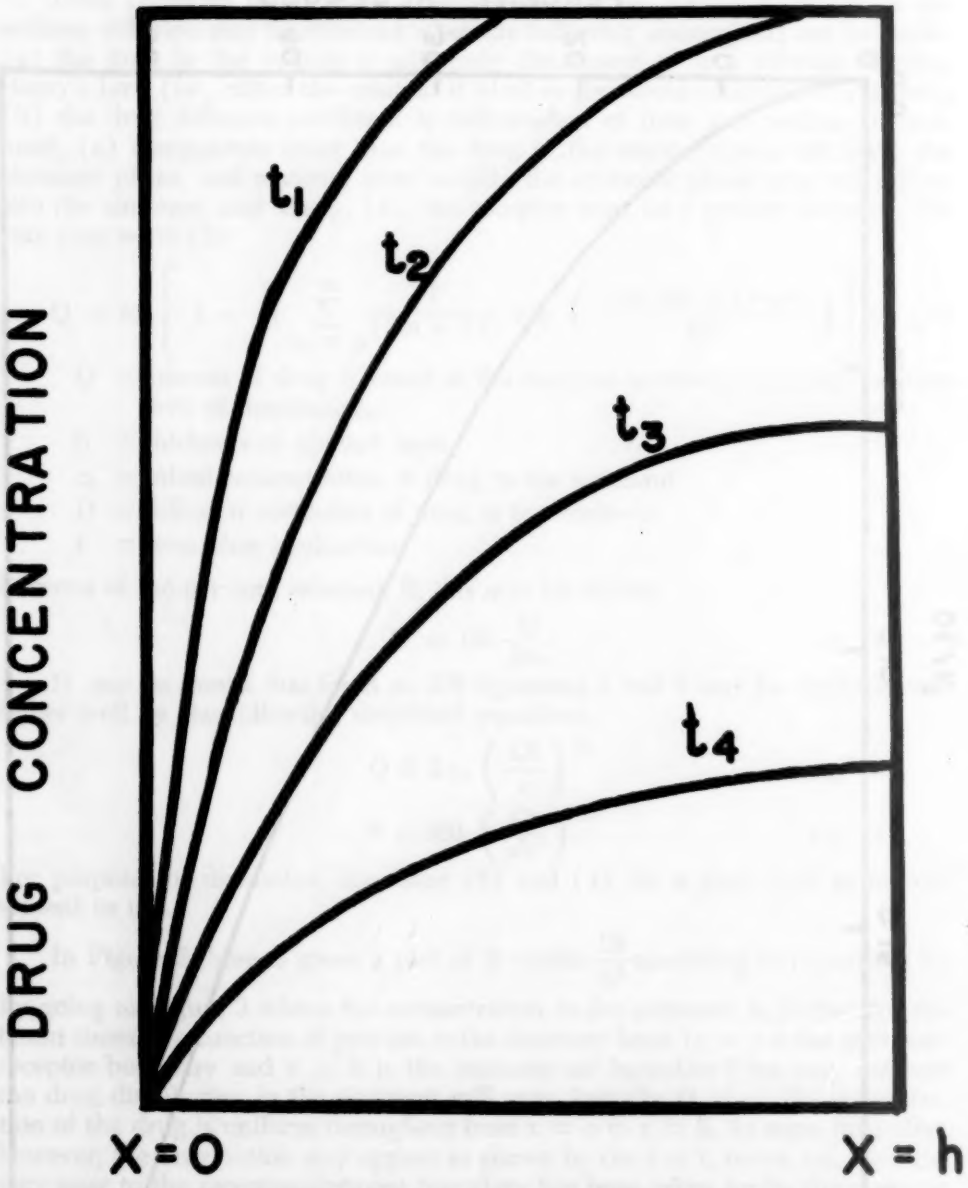

Figure 3.—Concentration profiles in ointment layer, diffusion into perfect sink at X = 0. Fick's Law behavior.

and both the amount and the rate of release is directly proportional to this quantity. The other, the diffusion coefficient, now requires some discussion.

If the ointment base is itself a liquid or solution composed of molecules of size comparable to or smaller than the drug molecule, the value for the diffusion coefficient is rather well approximated by the Stokes-Einstein equation,

$$D = \frac{kT}{6\pi va} \qquad \text{eq. (5)}$$

where k is Boltzmann's constant, T is the absolute temperature, a is the molecular radius of the drug (can be estimated from the molecular weight and the density of the drug), and v is the viscosity of the ointment. If, therefore, the ointment viscosity is that of water, D values would range from about 1×10^{-5} to 1×10^{-6} $cm^2\ sec^{-1}$ for most drug molecules (note that a is in general proportional to only the cube root of the drug molecular weight). Thus, according to equations (5) and (4), in a matter of minutes a sizeable fraction of the total amount of drug would be released from a one mm. layer of such an ointment to a *good* receptor.

Most ointment bases are not as simple as the one described above; the problem of estimating D becomes quite difficult. In the case of emulsion and suspension type vehicles, approximate relationships are available which relate the effective drug diffusion coefficient for this type of vehicle to the volume fractions of the phases and to the diffusion coefficients and partition coefficients of the drug in each of the phases comprising the heterogeneous system (see Figure 4). One of these expressions is

$$D_e = \frac{D_1}{V_1 + KV_2}\left[1 + 3V_2\frac{KD_2 - D_1}{KD_2 + 2D_1}\right] \qquad \text{eq. (6)}$$

D_e = effective diffusion coefficient of the mixture

D_1 = diffusion coefficient in the external phase

D_2 = diffusion coefficient in the internal phase

V_1 = volume fraction of the external phase

V_2 = volume fraction of the internal phase

and K = equilibrium partition coefficient, defined as

$$K = \frac{C_2(\text{conc. of drug in phase 2})}{C_1(\text{conc. of drug in phase 1})} \qquad \text{eq. (7)}$$

Equation (6) assumes that Fick's Law must apply to either of the two phases. Furthermore equation (6) is expected to be quantitatively applicable only for systems of dispersed spheres at small V_2 values ($\cong 0.1$). For larger V_2 values and for systems involving highly asymmetric particles this expression is only qualitatively applicable. Other expressions should then be considered (4). For the present purposes equation (6) will suffice to illustrate the behavior of a filler when the system as a whole obeys Fick's Law.

From equation (6) it can be seen that if K is small compared to unity (drug preferentially partitions into phase 1) and if D_2 is comparable to D_1 (as is usually the case for emulsions), then the internal phase acts mainly as a mechanical barrier within the ointment. This situation will not make D_e much smaller than about $0.5\ D_1$ for most values of V_2. Thus, from the drug release point of view such fillers do little to alter the picture. On the other hand, if K is large compared to unity (drug preferentially partitions into the internal phase) D_e can be made smaller than D_1 by the order of $\frac{1}{KV_2}$. Thus, for a given C_0 [see eq. (3)] the release to a

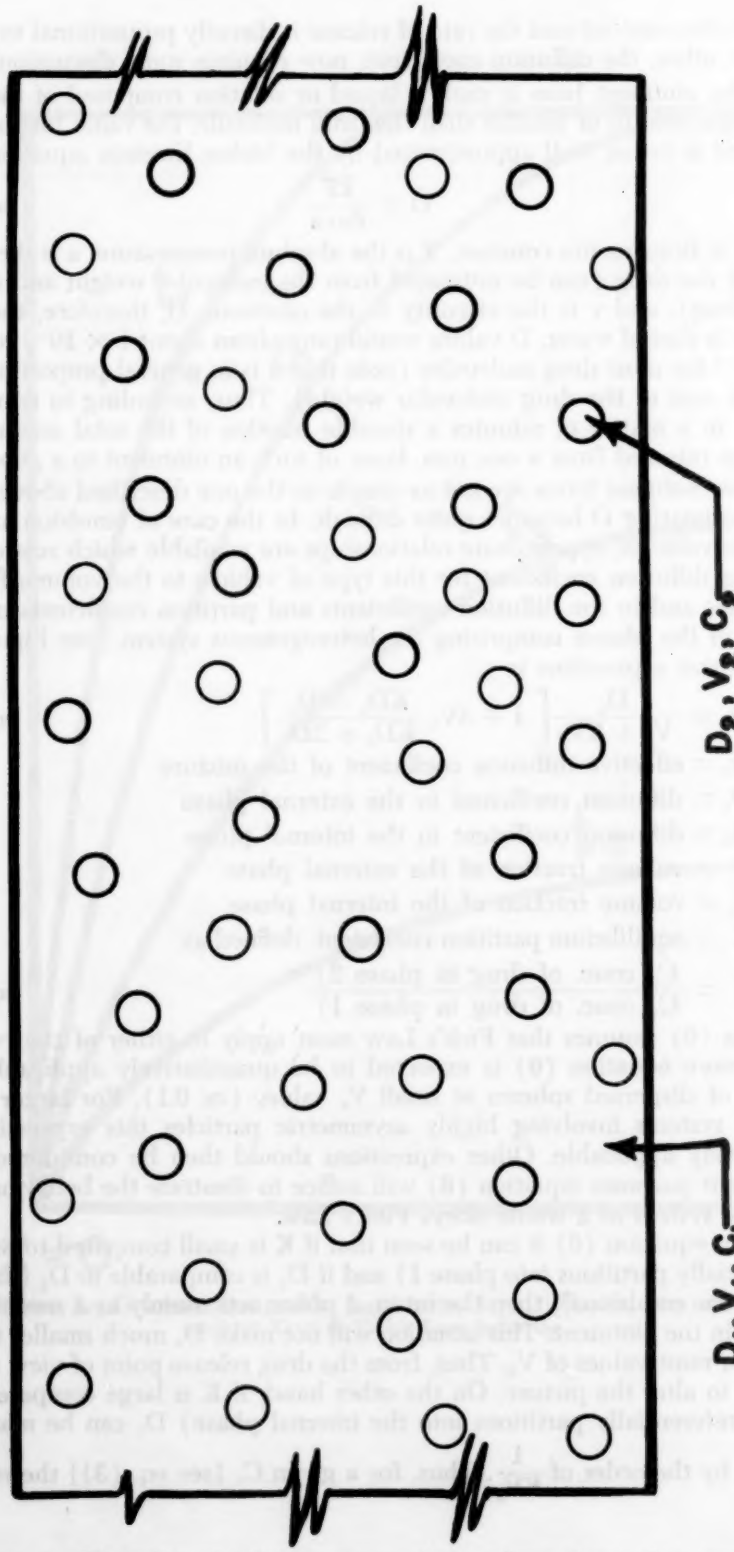

Figure 4.—Illustration of a heterogeneous ointment base. A two-phase system.

good absorber may be retarded by a factor the order of KV_2 if an emulsion base with a large K is used instead of a base made of the external phase material alone.

While the preceding interpretation of equation (6) involves partitioning of the drug into the internal phase, the equation may be used to calculate D_e for other situations of practical importance. If most of the drug is initially adsorbed onto particles of the internal phase and if the adsorption obeys a linear adsorption law (*i.e.* amount adsorbed is proportional to the concentration of the drug in the external phase) equation (6) may be used; but, with

$$K = \frac{M_2(\text{weight of drug adsorbed per unit volume of adsorbent})}{C_1(\text{weight of drug per unit volume of external phase})} \quad \text{eq. (8)}$$

Now the Langmuir adsorption equation is, in general, a good first approximation for many cases in which there is solute adsorption onto a solid from solution. It can be written

$$m = \frac{M_2}{\rho} = \frac{k_1 k_2 C_1}{1 + k_1 C_1} \quad \text{eq. (9)}$$

where m is the amount of adsorbed drug per unit weight of adsorbent, ρ = density of the adsorbent, and k_1 and k_2 are the usual constants. It is apparent that this equation may be approximated by a linear isotherm when $k_1C_1 << 1$, viz.

$$M_2 \cong \rho\, k_1 k_2 C_1 \text{ when } k_1 C_1 << 1 \quad \text{eq. (10)}$$

Thus, equations (6) and (8) may be used with $D_2 = 0$ for most situations in which no more than a monolayer of drug is initially adsorbed. It should therefore be possible to predict* rates of release from appropriate adsorption data. For these simplified relations to hold, it is important that most of the drug in the ointment exist in the adsorbed state. This case is, of course, the interesting one anyway. It can again be seen that an adsorbent possessing a large K value would retard release by the order of KV_2.

Another application of equation (6) may be found in situations where immobile complexing agents, such as certain polymers possessing suitable functional groups, may bind drug according to a linear binding law†. In this case, equation (8) may again be used with "adsorbent" being replaced with "agent" and with

$$M_2 = kC_1 \quad \text{eq. (11)}$$

where k is the binding constant. Again, for these relationships to apply, it is necessary that most of the drug in the ointment is in the bound state* (as are most of those examples in reference 5).

While we are on the subject of polymers, it appears to be worthwhile to discuss the meaning of D_1 and D_2. Unless the polymer is very concentrated and highly crosslinked continuously in the ointment base (this is never the case), it may be presumed that a diffusing drug molecule experiences relatively little mechanical resistance due to the presence of the polymer chains. Thus generally

$$D_e \cong D_1 \cong D_2 \quad \text{eq. (12)}$$

An example of this situation is Jelene which consists of mineral oil jellied with polyethylene. While the macroscopic viscosity of this base is quite large, the vis-

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* This type of approach has been used in the development of protective ointments, see reference 2.

† See, *e.g.*, reference 5 where there are given a number of examples of binding according to linear law or near linear law at low concentations.

* Here and in the previous example of absorption, if most of the drug is not in the bound state and if the drug concentration in the external phase was much higher than necessary for essentially full coverage one would get deviations from equation (1) in the direction of getting somewhat less released at small times and somewhat more released at later times than predicted by eq. (1).

cosity as experienced by the drug molecule should be essentially that of mineral oil (or perhaps less if the drug molecule is small compared to the mineral oil molecule)†. Thus, the effective diffusion coefficient, in the absence of any binding, would probably be given by equation (5) with v being the order of the viscosity of mineral oil.

Having considered the theory appropriate to this section, let us present an example from the *in vitro* release studies by Patel, Banker, and DeKay (6). These investigators studied the rate of release of sodium radio-iodide from various hydrophilic ointment bases which differed only in the kind and amount of surfactant used. The other ingredients in the base and their amounts were essentially the same as those in the official hydrophilic ointment described in U. S. P. XVI. In Figure 5, the release data (circles) are given. The smooth curves represent theory as predicted by equation (2) with, however, a different D value for each of the four curves chosen to give the best fit to the particular set of data. The test of the theory in this case applies, therefore, mainly to the time dependence of release. In general, the agreement is very good, suggesting that the conditions for the applicability of the theory of this section to their experiments were well approximated (see the assumptions in the first part of this section). It is significant, furthermore, that the effective D value giving the fit to the data for Sipon ES, 1%, differs by only the order of a factor of two from the theoretically calculated D_s according to an equation similar to equation (6). In this calculation, it was assumed that the oil phase in the base was impermeable to sodium iodide and that therefore the sodium iodide diffused in the aqueous phase only (7). Thus, the agreement of the data with theory as a whole is also satisfactory.

Drug Diffusion in Ointment Not Obeying Fick's Law. When any of the underlying assumptions of the theory in the previous section are not true for the ointment, equations (1–4) may not describe the behavior of drug release from the ointment. There are a number of practical situations in which assumption (a) of the previous section will not apply but for which an alternative approximate equation is available. These cases are the suspension type formulation and certain types of bound-drug formulations. We may write (3) in these cases

$$Q = [C_s(2A - C_s)\,Dt] \qquad \text{eq. (13)}$$

$$R = \frac{100Q}{hA} = \left[\frac{h^2A^2}{C_s(2A - C_s)}\,Dt\right]^{1/2} \qquad \text{eq. (14)}$$

where A is the total drug concentration (free drug plus solid or solid complex drug) C_s is the "free' drug concentration in equilibrium with solid drug or solid drug complex and the other symbols are the same as before. Equations (13) and (14) apply to systems in which the concentration of the free drug (which is the only diffusing species) in equilibrium with the total drug is independent of the amount of the total drug. Thus C_s might be the solubility of a drug which would be independent of the amount of solid drug present (provided solid solution does not form). Also some types of drug binding by polymer appear to approximately follow this kind of behavior in certain concentration regions. For example, the iodine-polyethylene glycol system (8) appears to give this behavior (in this case C_s would be the iodine concentration in equilibrium with the complex). Solid solvates may also fall in this category.

† See reference 1 for this type of interpretation of data.

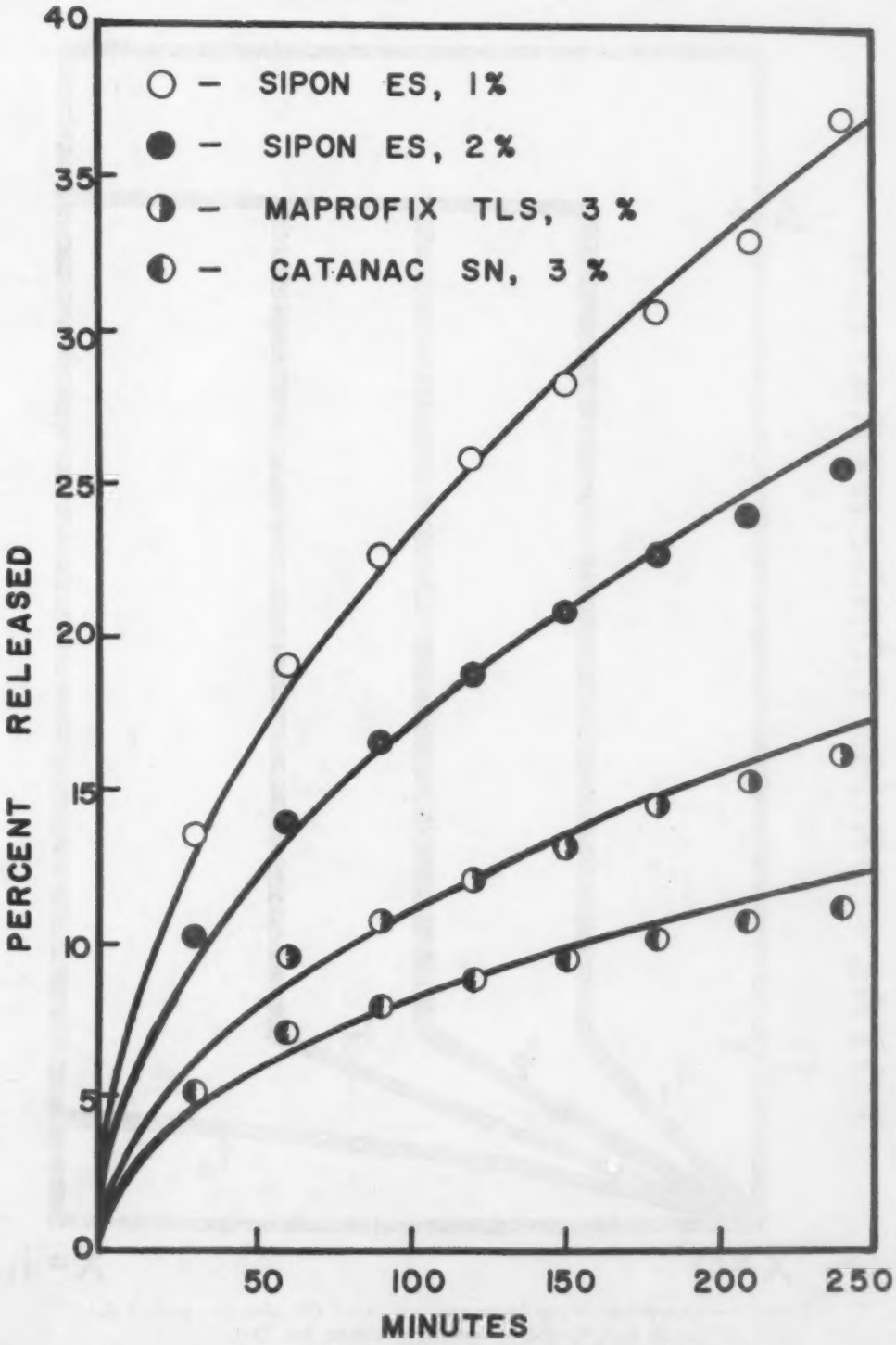

Figure 5.—Sodium radioidide release from hydrophilic emulsion ointments. Circles represent data, curves represent theory. See Text.

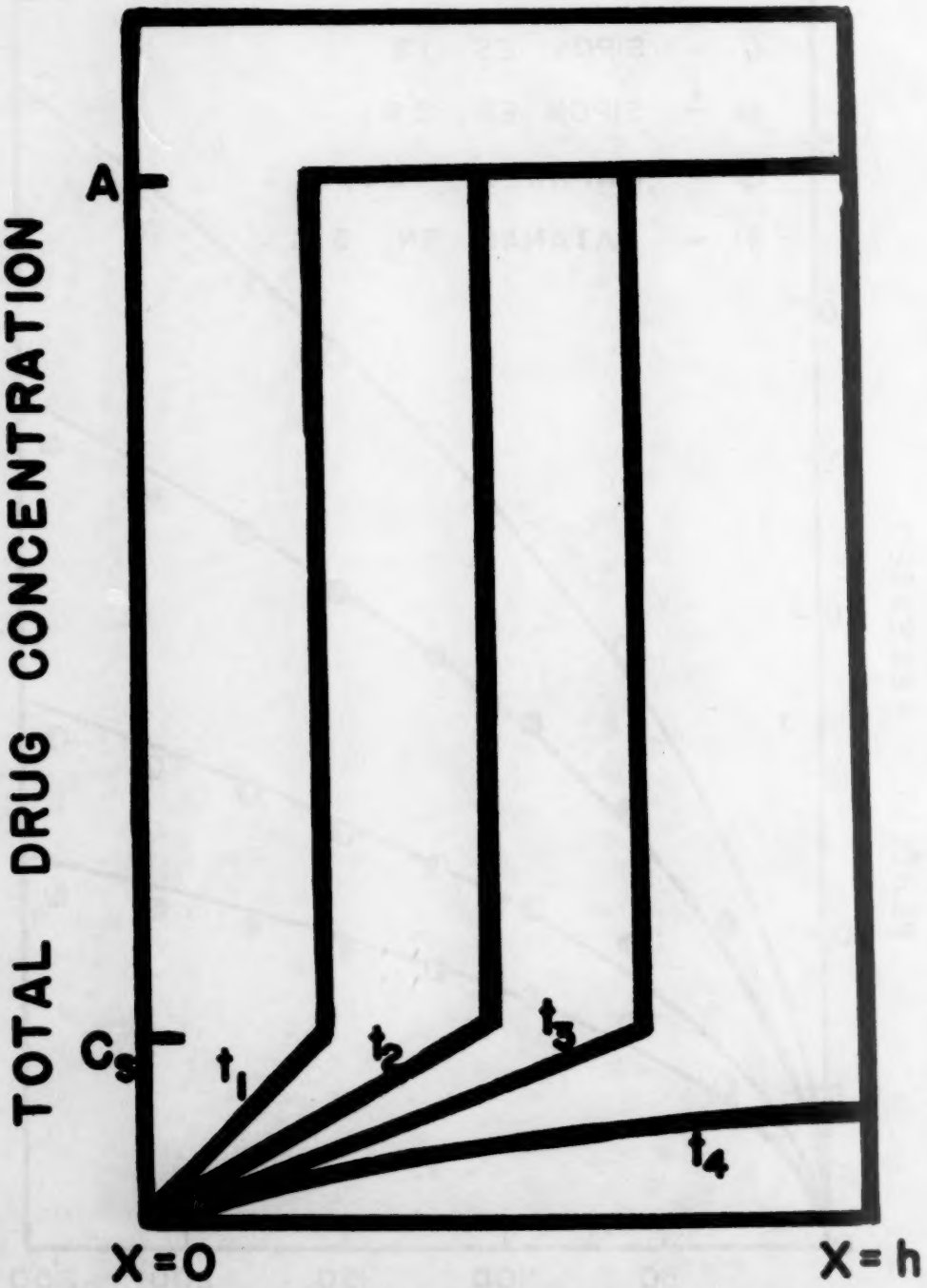

Figure 6.—Concentration profiles in ointment layer, diffusion into perfect sink at X = 0. Suspension type ointment. See Text.

In Figure 6 the drug distribution during release is illustrated for these cases. The situation may be said to be a "moving boundary" type of diffusion. The boundary recedes only as fast as the free drug molecules can diffuse out. Note that until the boundary has reached $X = h$, the concentration gradients between $X = 0$ and the boundary will be essentially linear as long as $A >> C_s$).

It is apparent by comparing equation (3) with equation (13) what similarities and differences might be expected in these two cases when the same amount of drug is in the ointment. The time dependence in both cases will be essentially the same, *i.e.* the square root dependence. But if $A >> C_s$ (which is the interesting case) and if the D values are the same for both, the rates of release will differ by a factor

$$\left(\frac{2\,C_s}{A}\right)^{1/2}$$

It must be cautioned again that this applies to the case where the receptor is a perfect absorber; because if the rate determining step is penetration of the receptor itself, there may be no differences at all. In fact in this latter case, a suspension type ointment may be the faster releasing of the two, because then the thermodynamic activity of the drug becomes the important factor.

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PERCUTANEOUS ABSORPTION

KENNETH M. WILSON

An ever increasing fraction of the literature dealing with the properties of skin is concerned with "percutaneous absorption" but judged from a rigorously scientific point of view, widespread interest in the topic is fairly new. Nevertheless, several classic publications appeared over a quarter of a century ago among which those of Schwenkenbecker (1), Frey and Rein (2) on the physiology of skin and Rothman and Schaaf (3) on the chemistry of skin are outstanding reviews while Rothman's book (4) on the Physiology and Biochemistry of Skin, published by the University of Chicago in 1953 remains a "Vade Mecum" for interested investigators.

A noticeable feature of publications dealing with percutaneous absorption is the tendency to fashions in respect of the materials studied; in the late '20s and early '30s these were mercury and salicylates, in the '40s allergens, while in the early '50s "war work" on vesicants and nerve gases was described together with some data on the absorption of sulphonamides. Currently, much interest is being shown in the absorption of hormones and other cosmetic adjuvants and this trend is likely to continue.

The post-war work brought with it a much extended methodology in which the use of radio-active isotopes is pre-eminent and because these techniques have yielded much new knowledge, this paper will necessarily make extensive reference to work carried out with their aid.

Before going further, some often misused terms should be defined: *"Percutaneous Absorption"* means absorption by way of the skin and therefore implies that some material reaches the circulation. *"Penetration"* implies that the drug or other material overcomes some obstacle in the way of its free passage. The term will be used in this quasi-military sense. *"Permeation"* means that bulk material spreads more or less evenly throughout the structure being considered, i.e., in the sense that water "permeates" a sponge. *"Diffusion"* has its strictly physical meaning of the migration of molecules between other molecules.

When a section of skin is examined microscopically, the hair follicles and sweat ducts appear to be channels through which percutaneously applied material could reach the deeper layers, and the question as to whether these "defects" are the major route of percutaneous absorption is still a matter of investigation and debate.

Earlier work, based mainly on histological localization of applied dyes and other chemically detectable agents suggested that the transfollicular route could be the major one but some recent work by Tregear (5) demonstrated that isotopically labelled Tri-n-butyl phosphate applied directly to hair follicles of pig skin penetrated no more readily than similar amounts applied between the follicles. Tregear concluded from this and other data that "it seems probable that the protective impenetrability of (pig) skin is limited by the structure of the epidermis itself and not by sweat glands and hair follicles acting as holes punched in it".

This conclusion seems reasonable in view of the fact that the skin of palms and hands, containing many sweat glands is poorly penetrable (6) by many substances whereas the volar surface of the forearm is easily penetrated but has fewer sweat glands and usually no hair follicles.

Frederickson (7) made autoradiographs of cat skin treated with radio-active Parathion and found some accumulation of material in the hair follicles but stressed that this did not mean that the transfollicular route was the main one because the rest of his data indicated that transepidermal absorption was at least as likely. Frederickson also used Szakall's technique (8) to produce strippings from human skin, and found similar accumulation in follicles and sebaceous glands but felt that the auto-radiographs revealed the affinity of Parathion for certain structures and commented, "After all, it is an obvious fact that auto-radiographs of this kind show only what has *not* been absorbed".

When we think about the possible significance of follicles and sweat ducts as channels through the skin, we should remember that these are "holes" only in the sense that the stratum corneum, ("horny-layer") is substantially discontinuous at the orifices of these structures, since all are lined with epithelial cells continuous with those of the epidermis. We should also remember that in the human at least, the area of the follicular orifices is very small compared with the total skin area while the sweat ducts may be blocked, or if active, are likely to contain fluid flowing slowly outwards.

A good demonstration of the continuity of the hair follicles with the epidermis can be made by stripping a piece of excised skin with tape after the surface has been lightly scalded with water at about 70°C—the follicles are removed intact together with the epithelial layer.

Keeping these views in mind, we can consider other properties and components of skin and of applied chemicals as factors influencing percutaneous absorption.

The outermost layer—the "stratum corneum" has naturally received much attention. This layer consisting of the remains of dead epithelial cells is very variable in thickness and in its detailed composition, but as one of the several keratinized structures is a complex protein material containing a large amount of sulphur (nitrogen/sulphur ratio is about 4) and a variable amount of fatty material derived both from the original epithelial cells and from sebum. The sulphur in keratin is present mainly as di-sulfide links and together with hydrogen bonds and "salt bridges" make keratin a polymer.

Such a material if homogeneous, would be expected to be a nearly impervious barrier to most materials but in life the stratum corneum is, for the most part, flaky and discontinuous. The layers and cracks are visible in the light microscope, but are particularly strikingly shown in electron micrographs (9).

For this reason, topically applied solutions permeate the fissures quite readily and the bulk of the stratum corneum does not appear to be a major barrier to absorption of applied chemicals. Many definitive experiments demonstrate this, and among the most recent, those of Fredrikson again serve as a good illustration.

Fredrikson (7) applied radio-active Parathion (a cholinesterase inhibitor) to excised human skin contained in a moist chamber at 23–24°C and made 25 consecutive skin strippings from which he was able to show that while most of the agent remained in the first 4 or 5 strippings, some reached the 25th even if exposure to the Parathion was as short as two hours. Only after 24 hours exposure

could the radio-activity be demonstrated to have spread below the epidermis and around the follicles.

Fredrickson's recent experiments provide still further evidence that a major barrier to penetration of skin is to be sought between the dead stratum corneum and the living epidermis. This concept put forward by H. Rein nearly 40 years ago (10) is supported by a massive body of evidence and after much dispute is now becoming generally accepted.

Rein's work led him to name the "stratum lucidum", (a thin hyaline layer usually demonstrable by appropriate methods at the boundary of the epidermis and stratum corneum) as the site of the barrier and the recent electron microscopy by I. Brody (9) has shown some interesting features of the transition layers at this point. Brody's observations are likely to be significant in the further study of the skin's barrier layer, especially in relation to the influence of keratinization.

Confirmatory evidence of a different kind is suggested by some briefly reported experiments of Marzulli and Tregear (11). These workers stripped stratum corneum layers from excised human skin until they obtained continuous sheets of so called "stratum corneum conjuctum", corresponding to the coherent layers of dead epithelial cells lying immediately over the living epidermis. Marzulli and Tregear showed that this layer of compact keratin was about as good a barrier to the penetration of labelled Tri-n-butyl phosphate as was unstripped isolated epidermis, but because stripping of keratin from this tissue only increased the penetration rate two-fold, they postulate a further barrier below the stratum corneum conjuctum. Such a site would correspond, at least approximately, with the histologists "stratum lucidum" and would seem to be the same as Brody's transitional layer.

Taking this and other available evidence into account, we could make the reasonable assumption that the "barrier layer" results from the dying or just dead outermost layers of epithelium and that its formation is connected with the process of keratinization: this assumption would, in effect, be a more specific statement of the earlier postulates of Rein (10) and Rothman (3, 4).

If we accept the presence of a barrier of the kind and in the location outlined above, we must next consider the physical and chemical properties of both the barrier and the "penetrating" substances.

Rein's original experiments[2] demonstrated that electrolytes and many dyestuff ions could not penetrate beyond the base of the horny layer. This fact has been confirmed many times and suggests that the barrier may be lipoidal particularly since a number of "oily" (e.g. Methyl Salicylate) (12) substances are known to penetrate skin fairly readily.

The presence of substantial amounts of lipids in stratum corneum has been mentioned but it should not be forgotten that this material can also take up water. In fact, hydration is the main variable determining the softness and flexibility of the stratum corneum as was so elegently shown by I. Blank (13) some years ago, and the state of hydration at the barrier layer might well contribute to its effectiveness.

In the more recent literature on this subject, the experiments of Treherne (14) on the permeability of skin to a range of nonelectrolytes yielded important data. Treherne was able to show among other things, that the penetration of excised rabbit skin by these substances was related to the ether water partition coefficient and that the optimum penetration occurred with a coefficient close to one (1). A mathematical analysis of the data led to the conclusion that the bar-

rier layer might be a layer of water sandwiched between two lipoid layers, and that a close packed layer of cells of which the membranes would be the lipoid layers and the cell contents the aqueous layer would satisfy the conditions. Treherne suggested that the stratum granulosum could be the layer involved but did not indicate that living cells were a necessary feature. In fact, his criteria can be satisfied by a "dead" system and it seems more likely that the apparently just dead cells of Brody's transitional layer will prove to be the main barrier.

It is certainly true that if skin strippings are made down to the stratum granulosum, or if a fine scratch is made just through the "barrier", the penetration of non-ionic substances is markedly increased (15). Since the bulk of the epidermis containing the most viable cells is left intact by either technique, these living cells cannot fully account for the impedance to the penetration of all substances.

An interesting and very appropriate theoretical physico-chemical analysis of inert oil/water systems as rate controlling mechanisms has been made by Higuchi (16). Higuchi's analysis is directed as much towards the influence of ointment bases on penetration as towards the properties of skin but the data considered is equally applicable to the cellular derived lipoid/water system. It is shown for instance, that the thermo-dynamic activities of the solute in the two phases determine the concentration gradient (i.e. the rate of penetration).

Higuchi also pointed out that these properties of an "ideal" system can be modified by the state of hydration of the protein components of any "barrier" and quotes the effect of relative humidity on the penetration of glyceryl monostearate by way of example.

The analysis just mentioned does in fact parallel and support Treherne's conclusions, or to quote Higuchi, "This may lead to selection of a compound having balanced hydrophilic/lipophilic properties if the double barrier layer such as suggested above really exists".

Apart from the demonstrable barrier in the region of the stratum lucidum, we should next consider whether the epithelial cells are themselves a barrier to the movement of chemicals towards the underlying capillary bed.

In 1935, Danielli and Davson (17) proposed a model for the membrane of red corpuscles, which consisted essentially of a water-oil-water sandwich, and in the intervening years this proposition has been substantially validated though it is certain that the membrane is much more complex than the simple model. Nevertheless recent electron micrographic studies of many different cells show the ubiquity of a double lipophilic layer with a space, probably hydrophilic, between them.

These recent findings provide increasing evidence of the involvement of lipid barriers to the penetration of non-lipid soluble substances and lend considerable support to the much earlier, general theses of Overton (18), and Collander and Baerlund (19).

The subject is very extensive but several pertinent reviews are available for the interested reader (20) as well as the papers by Treherne (14), Tregear (5) and others.

Dr. Schanker has given us a most interesting survey of this matter in the light of his own studies (21) and I would like now to mention a rather unique part of the integument which is particularly suitable for the study of penetration of epithelial cell layers.

I refer to the cornea of the eye, which is closely analogous to skin and has a common embryological origin.

Histological sections of this organ show the epithelium to be a five or six layered structure; free from "defects", overlying the substantial propria, which can be regarded as corresponding to dermis, especially in its major physico-chemical properties. The system is completed by a single layer of endothelial cells, so that it forms a "thick membrane" oil-water-oil arrangement as well as a convenient source of homogeneous epithelium without a definite horny-layer.

There are a number of important contributions to the study of penetration of drugs into the eye and these are to be found in the ophthalmological literature (22) but two particular investigations are especially appropriate for the present discussion.

In 1942, Swan and White (23) studied the penetration of a number of substances into the eye and their work called attention to the importance of the physical properties of these substances (e.g. polar/non-polar compounds) in determining phase solubility and the latter's relation to penetration.

In 1944, Cogan and Hirsch (24) made a definitive study of the penetration of weak electrolytes and their demonstration that the ability of substances like aniline to penetrate the cornea was a function of pH and the degree of association of its salts is particularly elegant. Kinsey (25) has suggested a very reasonable scheme for the penetration of weakly basic drugs like homatropine through the three layers and this has been confirmed by the writer's experience with the cornea as a model system (26).

From experiments such as these, it is now definitely established that the impedance offered by epithelial cells to salts of weak acids and bases is a function of phase solubility and that in a biphasic system, penetration is favored when the drug or other chemical is soluble to some degree in both phases. With dissociable substances this may involve changes from associated to dissociated forms as the chemical encounters each successive phase.

Higuchi's analysis can be applied to these systems and is shown to be plausible and adequate to explain the experimental results.

We come now to the dermis, that is, the structure composed mainly of collagenous fibers upon which the epidermis and associated structures grow.

The main component of dermis significant in percutaneous penetration is undoubtedly the papillary layer with its elaborate capillary plexuses, but since these lie immediately adjacent to the basal layer of the epidermis, substances penetrating trans-epidermally are not impeded by the bulk properties of the dermis. Any impedance that does exist is most probably due to the properties of the basal membrane and of the capillary walls.

Such studies of the properties of the dermis as a barrier to penetration as have been made (14) indicate that it behaves as a large-pored membrane and that simple diffusion through liquid-filled channels accounts for the quantitative aspects of diffusion through it.

It seems that the bulk properties of the dermis could only be of importance if the major route of penetration of a given chemical is through the "defects"—particularly the sweat ducts and the evidence for this is mainly histological as for instance, that obtained by MacKee, Herrman, Baer and Sulzberg (27).

In summary, the present situation in respect of the general aspects of percutaneous penetration may be stated briefly thus:

Apart from frank damage caused by the applied agent, the penetration of a given substance is dependent upon the physico-chemical properties of the agent

and of the skin components taken together with the anatomical arrangement of the latter.

Physico-chemical properties of major importance are lipid solubility and the oil/water partition coefficient with pH in both the bulk phase and at the cell membrane as an important determinant in the case of dissociable substances. Solubility in both oil and water favors penetration.

Anatomically, the transition layers between the living epidermis and the dead stratum corneum are probably the site of the main barrier to penetration, but the properties of the epidermal cells are contributory in determining rates of penetration.

The dermis is probably of small significance as a barrier and the role of hair-follicles and sweat glands is equivocal. In the human, the hair follicles are, for the most part, of minor importance and there is little evidence that the sweat ducts are a major route of entry.

It must be stressed here, that this simple picture of percutaneous penetration should be regarded only as a background.

Many detail variations are known both in the anatomy of skin from different areas and in the properties of particular chemicals and these variations can provide contradictions.

An especially important consideration is the effect of the chemical on the tissue elements through which it passes and though this may not produce obvious damage, metabolic and other changes can be promoted which in their turn, affect penetration rates.

Mixtures or sequential applications of two compounds can also seriously alter penetration rates of one or both, e.g., chemical depilation of skin usually results in markedly increased permeability to many substances.

A physiological factor of prime importance to the overall rate of penetration concerns the blood-flow through the skin capillaries since this determines the rate of clearance and therefore the concentration gradient. Because of this, substances which alter the vascular status can affect their own rate of absorption into the circulation as seems to be the case with Methyl Salicylate, among others. (13B)

NOTE ON METHODOLOGY

Many of the ingenious techniques used in the study of skin as a barrier to penetration are described in the literature referred to previously and some specialized ones of importance are illustrated by the film prepared by M. Ainsworth[80] and his colleagues at the Chemical Defence Experimental Establishment, Porton, England. These sources should be consulted for further details and extensive references to other work.

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SUMMARY AND EVALUATION

SUMMARY AND EVALUATION OF WORKSHOP IN DEPTH ON THE FIRST COURSE IN PHARMACY

MITCHELL J. STOKLOSA

In presenting the summary and evaluation of the Workshop in Depth for the first course in the area of pharmacy, I should like, first of all, to emphasize the following points.

1. The attendance at this morning's session was excellent.

2. There was a very active participation by the seminarians in the various phases of the discussion.

3. As in all discussions dealing with course objectives, course structure, and course content, there were differences of opinion; there were mutual agreements and strong disagreements; and yet, there was an air of interest and enthusiasm that prevailed throughout the entire discussion.

In my opinion, an over-all assessment of the meeting would seem to indicate that the discussion was fruitful and beneficial. When Co-chairman Lemberger invited me to present the summary of this workshop, he stated that it was his hope that, as a result of the morning session, a detailed syllabus for the course could be prepared. Although it is not possible to present a detailed syllabus to you at this time for evaluation and comment, it is gratifying to note that the group has come to some very definite conclusions relative to course content, objectives, and prerequisites. These will be presented as part of the summary. I am sure that I express the sentiments of the other seminarians who attended this morning's Workshop in Depth when I say that we all learned some things, and that we are going back to our schools and colleges with a few new ideas that can be adapted to our present course structure in the interest of revision and improvement.

In general, the discussion of this session was based on the comments that were made and noted in the workshops which were held earlier in the week. The specific topics relating to the syllabus that were considered by the group and the different opinions that were expressed concerning these points may be summarized as follows:

1. **Integration.** There was considerable discussion relative to the advisability of integrating the first course in pharmacy with the courses at the next levels of instruction. Some felt that the technical courses at the three levels should be combined; others expressed the opinion that such an arrangement would not be a compatible one. Although there was some disagreement as to the degree of integration or correlation of these courses, the over-all thinking of the group seemed to indicate that the first course should be taught as a preparations course with an integration of relevant physico-chemical principles on a qualitative basis. A plea was made for the presentation of the material in the first technical course at a more challenging level.

2. Objectives. The summaries of the workshops held earlier in the week suggested a need for a restatement of the objectives of the course. The participants in this morning's discussion agreed that the objectives should be restated to read as follows:

a. To introduce to the student the physico-chemical principles, at a qualitative level, that are peculiar to the field of pharmacy and which are basic to the manufacture of pharmaceutical preparations.

b. To study the classes of pharmaceutical preparations with emphasis on the class as a whole.

c. To develop the essential skills and techniques for preparing various forms of medication.

d. To gain a familiarity with pharmaceutical terminology.

3. Classification. There was an expression of opinion concerning the order and manner of listing the various classes of pharmaceutical preparations. While it was felt that there might be more than one acceptable system of listing these classes, it was generally agreed that it would be feasible to use an approach that would suggest a logical relationship of one class to another. It was agreed that a presentation using the so-called "liquids-solids-heterogeneous systems" classification would provide better organization and would enable the student to more readily recognize relationships between classes.

4. Prerequisites. The matter of prerequisites for the course was considered by the group. It was generally agreed that the prerequisites and/or corequisites for the first technical course in pharmacy should include organic chemistry, physics, and pharmaceutical calculations.

5. Large Scale Manufacturing. There was a division of opinion concerning the advisability of presenting large scale manufacturing at this level except, possibly, on a demonstration basis. Accordingly, no mutual agreement was reached relative to the inclusion of this topic in the course outline.

These comments represent, in summary, the discussion of this morning's Workshop in Depth for the first course. It is hoped that there have been no significant omissions on my part and that the summary is entirely compatible with the over-all thinking of those who participated in the discussion. Should there be any additions to this report, comments to that effect by those who were in attendance this morning are now in order.

WORKSHOP IN THE SECOND COURSE IN PHARMACY PHYSICAL CHEMICAL PRINCIPLES IN THE PHARMACEUTICAL SCIENCES

EDWARD G. RIPPIE

The "Second Course in Pharmacy" as presented here refers to a body of knowledge rather than to the second of a series of courses given in a particular curriculum. This workshop served, therefore, to determine the depth to which the fundamentals of physical chemistry should be taught so that the practical applications can be understood more thoroughly.

The depth of study suggested in this workshop was intended to serve only as a guide, and it was realized that many schools at present are unable to devote the time required for this coverage.

During the period allotted for discussion, the general topics of structure of matter, thermodynamics, kinetics, colloid chemistry, and solution chemistry were discussed. It was felt that the subject matter to be covered under these general headings should not be restricted to that for which there are known pharmaceutical applications. Such a restriction would be undesirable for two reasons: (1) it would seriously limit the general educational value of this material and (2) future developments may well embody principles not used at the present. While these reasons are obvious, they seem worth mentioning here.

It was pointed out that, while the structure of matter is considered in inorganic and organic chemistry courses, the material should be reviewed on a more advanced level. A thorough knowledge of atomic and molecular structure and the forces involved is requisite to an understanding of many of the phenomena encountered in practice. The subject should include material on quantum theory and the electronic configuration of the elements, molecular orbital theory, and the nature of binding forces between molecules as they exist in the gaseous, liquid, and solid states.

Thermodynamics is of such a fundamental nature as to warrant a thorough treatment employing pharmaceutical examples where applicable. A firm understanding of the three laws of thermodynamics and their basic physical chemical implications should be acquired. These principles can then be applied in the same or subsequent courses to an understanding of colligative properties, electromotive force, chemical equilibria, surface phenomena, etc. Opinion was divided on the approach to be taken in teaching this material. The classical approach was favored by some, while others believed that the acquisition of a physical concept of the various thermodynamic functions was more desirable. Those who favored the classical treatment felt that after working with free energy, enthalpy, entropy, and the other common functions, the student would develop feeling for these quantities without any particular attempt by the instructor to promote such an understanding.

Since a knowledge of kinetics is essential for an understanding of drug stability as well as for an understanding of bodily absorption and elimination times in connection with duration of action data, this subject received consider-

able interest and discussion. The student, it was felt, should be familiar with the derivation of simple 0, 1, 2, and 3 order rate expressions, though it was generally thought that he need not be able to derive them himself. The student should, however, be able to apply these expressions in predicting residual drug activity from simple kinetic data. Such an ability would enable him to better evaluate for himself the literature furnished with new products as they appear on the market.

The subjects of solution and colloid chemistry were thought to be of sufficient fundamental importance to be taught as individual subjects, but not necessarily in different courses. These subjects should include discussion of ionic equilibria, Raoult's law, Henry's law, activity coefficients, colligative properties, phase diagrams, electrochemistry, solubility, Donnan equilibria, and sedimentation. The emphasis on the particular topics would depend upon the instructor. In this way the basic theories and concepts could be learned most efficiently and would serve as a valuable background for subsequent courses.

It became evident early in the discussion that the suggested depth to which these topics were to be covered would require mathematical preparation beyond college algebra and trigonometry and would necessitate a knowledge of calculus. Grounding in statistics and probability theory would also be desirable. This mathematical preparation would serve not only as valuable background material for use in later courses, but also would be valuable in rounding out an often neglected facet of the general education of the pharmacy student.

Throughout the discussion, there was a marked tendency to favor a formal presentation of the subject matter and reserve many of the pertinent applications until a later professional course where they could be treated more deeply with no interruptions required for the presentation of necessary theoretical background. The material discussed here is worthy of a substantial amount of class time for its presentation and discussion. Accordingly, it was felt that, ideally, a full year of study (four credits per semester or quarter) with a total of eight semester or twelve quarter credits would be required.

WORKSHOP SUMMARY—THE THIRD COURSE IN PHARMACY

A. P. LEMBERGER

Although a proper evaluation of the workshop would be very dependent upon the objectives we place for it, I believe that those of us who participated in the session dealing with the Third Course in Pharmacy would agree that it was successful. Certainly, if we specify the exchange of information and the expression of viewpoints and ideas as a primary objective, the session was highly successful. On the other hand, if we had hoped to develop a syllabus for the third level of instruction at the workshop this morning, our success was quite limited.

This result might well be expected, however, because the nature of instruction at this level in the pharmacy curriculum is somewhat ill defined and highly dependent upon the approach taken in the presentation of the material preceding it. Thus, if one approaches this level of instruction with a background of physical-chemical principles taught as a separate course, the concept of subject content for the third course is quite different than it would be if a sequence of physical-chemical concepts integrated with technology formed the base upon which to build.

For this reason, some time was spent in discussing the relative merits of separating material into physical pharmacy and technology courses, and of integrating these into one course or sequence of courses. In the latter case, this course or sequence of courses would comprise both the second and third level of construction as we have attempted to delineate them in this seminar. As usual in discussions of this type, no definite conclusions were reached, but as a by-product of our discussion, we did establish the fundamental nature of physical-chemical principles to the meaningful consideration of technology.

In order to further our discussion, we then agreed to approach the subject as a level of instruction, rather than as a specific course. We further assumed that the student would have completed or was taking concurrently his organic chemistry, quantitative analysis, biochemistry, inorganic and organic medicinal chemistry, physical chemistry principles, microbiology, and physiology. Thus, the discussion was aimed at elucidating the contribution of instruction in the application of previously mastered basic sciences to the total professional education of the pharmacy student.

To this end we established three objectives for this area of instruction. The first of these is interdisciplinary coordination from the viewpoint of applications to pharmacy. These applications are to be made on a quantitative basis.

The second objective established, not altogether defined as separate from the first, is bringing the student to a full understanding of pharmaceutical systems or dosage forms and the components of these systems. Upon completion of this phase of his education, the student should appreciate the importance and significance of the underlying concepts upon which the technology of a given system is based. He should have the ability to read, to understand, and to use the literature at his disposal regarding any aspect of the given dosage form be it physical, chemical, or pharmacological. Finally, the student should be in a posi-

tion for critical evaluation and judgment of the utility and selection of a given system as a carrier for the drug and its intended use.

Lastly, this level of instruction should provide the student with a suitable mastery of the techniques and manipulative skills of pharmacy, as well as instruction in the use of pharmaceutical equipment.

Turning from our discussion of objectives, we next focused our attention on the subject matter itself. We used the outline presented by Dr. Parrott as a starting point and found general agreement on the completeness of the course content as proposed by him. Thus, the major direction of discussion was toward a consideration of the depth of coverage to be attained in any given area.

As a specific illustration, the topic of viscosity was selected for discussion. We attempted to delineate the material to be taught under this topic, such as definitions, equations, methods of measurement, flow properties, etc. It was apparent, however, that our discussion was not as fruitful as we might have hoped it to be.

I believe that I would be accurate in reporting a general consensus of our group that there would be much interest in a discussion of the latter type. For such a discussion to be successful, however, close direction and maximum coordination will be required. It will also be necessary for each seminarian to approach the discussion table fully prepared to participate in the discussion and to contribute to its success.

In general summary then, I am happy to report the success of our workshop, particularly in regard to establishing objectives for pharmaceutical technology instruction and in pointing out an area for future discussion by the members of our group.

A SUMMARY OF THE WORKSHOP ON THE FOURTH COURSE IN PHARMACY

GLEN J. SPERANDIO

The Fourth Course in Pharmacy was discussed in detail by the four individual workshops and then considered once by these groups collectively. The major questions which were discussed were as follows:

1. Should the present courses in dispensing be changed:
   (a) in content and subject matter?
   (b) in emphasis placed on subject matter?
   (c) in depth of instruction?
2. Should the material presented in the fourth course be taught:
   (a) as a "conventional" course in dispensing?
   (b) as a new course or sequence of courses patterned after Autian's Syllabus?
3. Should the title of the course be changed to more clearly indicate the nature and scope of instruction?
4. How much time should be spent on the teaching of:
   (a) compounding techniques?
   (b) incompatibilities?
   (c) How should the laboratory portion of the course be handled?
5. How many total credits should the course count?
6. What role will the pharmacist play in society in the future? What actually are we preparing our students for?
7. What should be the objectives of this course?
8. A considerable variety of questions was asked about Dr. Autian's Syllabus, chiefly concerned with the depth to which subjects would be covered and the manner in which they would be applied to dispensing.

Most of us are in agreement about what the pharmacy student should have had as instruction in the area of pharmacy by the time he graduates; but there is considerable disagreement on *how much* of certain materials he should have and *how deeply* we should go into "physical pharmacy."

We talked a great deal about "communications"—the need for the pharmacist to be able to properly transfer his knowledge to those whom he serves. It is my observation that *communication* was the chief weakness of seminar participants. All of us have difficulty in communicating our true intent to our colleagues and consequently complete understanding of one another is difficult. In spite of this, we feel that the seminar has brought us closer together in a common cause—our desire to train properly qualified pharmacists.

The following conclusions were reached:

1. The fourth course in pharmacy applies the learning from all other areas to the dispensing of pharmaceuticals and consequently involves the application of subject matter from all previous courses. (It *could* be the course at the top of the helix, as suggested by Dr. Martin.)

2. The objectives should be:

(a) To help the student make practical application of his theoretical knowledge of the pharmaceutical sciences.

(b) To qualify the graduate as an authority on drugs
   1. in the preparation of extemporaneous dosage forms.
   2. in the evaluation of drug products.
   3. in coordinating and interpreting drug information and communicating it to his professional colleagues and the public.

3. The following guiding principles are suggested:

(a) Sufficient emphasis should be placed on compounding and manipulative skills, presuming that the student has had instruction and experience in the theory and basic techniques of preparing dosage forms.

(b) Increasing emphasis should be given to drug products, their evaluation, formulation, and clinical uses; and to medical terminology and communication skills.

4. In general, to accomplish the stated objectives, a minimum of eight semester hours' credit is needed.

5. The syllabus suggested by Dr. Autian was considered on the basis of merit rather than depth. The group agreed with the spirit of the outline, but was unwilling to accept it as a syllabus for any one course.

The Seminar was highly successful, well-planned, and organized. The Seminar Committee and people at Wisconsin have certainly set high standards for all future Seminars.

SUMMARY AND EVALUATION OF THE SEMINAR

MELVIN W. GREEN

When I came away from home, I felt rather gratified that I had not had to put in several hours grinding away on a paper for presentation, but for the last few hours I have felt rather envious of those of you on the program that were free from such duties as I have been faced with. To summarize this seminar is, in one sense, easy—in one word it has been excellent. It has been well-planned and conceived, excellently executed with a most fortunate choice of teachers and leaders, participated in by nearly everyone, and profitable to all.

This has been called a seminar in depth. I suspect that many of you found yourself in the position that I did, namely in finding the depth all too frequently over my head. I hasten to add that the fault is mine for not knowing how to swim, and I am mindful that probably no one ever really learns to swim without getting in deep water at least occasionally. I hope you join me in being grateful for having been thrown in water over my head a few times with the admonishment to sink or swim. I am a little bothered about this figure of speech, however, since I remember the advertisement showing the duck in water to which a wetting agent had been added!

I am going to camouflage my inability to evaluate critically the technical papers by reminding you that you probably do not want to review the detail since the papers are available to you in abstract form, and resort to a somewhat more philosophic approach related to the avowed objectives of the seminar, interwoven with some of my own pet biases.

Just as the fellow who said that he was starting on his second million dollars first because he had heard that the first million is the hardest to make, I am going to start with the second objective of this conference first, because it is the easiest for me to talk about. The second stated objective of this seminar was to contribute to the personal professional advancement of the seminarians.

In this realm we have had a feast. The appetizer was there, the relish tray, a good rich roast of beef with vegetables on the side, and the dessert all mellowed with the wines of good humor and fellowship and topped with a cup of the strong black coffee of stimulation. It has been a meal that I will remember for a long time and I believe each of you will, too.

As a teacher—and I don't ever like to consider that I have given up that role—I have been made keenly aware of the march of progress of facts and concepts that are continually before us; we, too, must be students if we are going to be scholarly teachers. Even old facts and old concepts must be continually reclothed if they are going to have fresh meaning to a new generation of students with a somewhat different relationship to the world than ours. If we do not have continuously refreshened outlooks, our students will become as lost as we.

The well-springs of many of these ideas are deeply seated in the past, but if it is true that man is the only animal that takes the universe to bed with him, it is the 1961 universe which our student must have as companion, for that is where he moves and has his being.

Each of us has found stimulus and guidance here in proportion to our capacities, our backgrounds, and our needs. The most sophisticated among us is leaving with an idea, an approach, a fact, a plan, or something to add to his professional stature. Many of us are leaving with some sense of frustration at our own inadequacies, but with at least a hint of where to begin to correct them and a dramatic realization that a point of view has been born which we will be living with for a long time, and that we must be sufficiently flexible to accommodate ourselves to it.

Our lecturers have been unusually clear and lucid in their expositions, but some of us sense that we will have to do considerable homework when we return. The homework will be easier for the fine explanatory lectures we have had. Some of us may have to dig pretty hard, but you have proved to us that the pot of gold is there.

From things many of you have said, and bits I have overheard in the halls, I believe most of you agree that this seminar has gone a long way toward the achievement of this goal of contributing to professional advancement; in fact, I personally feel sufficiently expansive to state that it is probably the most helpful in this regard of all of the seminars we have held to date.

The other specific objective of this seminar, according to Dr. Lemberger, has been "to produce a syllabus for technical pharmacy instruction, not as a course by course progression but, as an overall sequence of topics to be mastered by the pharmacy student as he proceeds from the beginning to the conclusion of his work in pharmacy."

Most of us will agree that this objective was not reached in the sense of receiving a neat, well-tied package, but we are not too discouraged about it, for the committee made it clear that they recognized that such a goal could not be achieved in a week—if ever.

Dr. Lemberger, in his introductory paper stated that, "More likely as we look back upon this week we will see that we discussed a number of subject areas, that as a result of these discussions we have re-evaluated some of our original thinking in regard to the relative importance of certain topics that we teach and that we have revised our approach, stressing certain topics a little more, deleting or de-emphasizing others and, in general, improving our courses." Dr. Lemberger, I for one, believe you are a good prophet!

In the educational aspects of the subject matter phase, there are certain features that I believe are worthy of recapitulation and review. First, we remind ourselves that we are pharmacy teachers and that we are instructing the young concerning the pharmacy of drugs and certain other related substances. In the past, this has been purely a descriptive matter. Pharmacy was galenical pharmacy, it was rather static, so static that the U.S.P., at that time clearly the Bible of formulation, was revised only decennially. Often, at least in retrospect, the revisions seem as though they were born of strain to be different for the sake of being different.

Pharmacy was and is a bridge from the physician to the patient. When such pharmacy shifted its position a bit, as it occasionally did, we repainted the bridge. Occasionally, to attempt to attract our students and, I suspect, to relieve us from ennui, we changed the color of the paint.

I am told that the Golden Gate bridge is so large that it is being painted continuously so that the project is never really completed. If the powers that be were to select different colors from time to time, it would present a peculiar pic-

ture, to say the least, as such color layers intermingled and over-lapped. Our pharmaceutical bridge has now become so large that it, too, needs continual painting and, because we find it advisable to change the colors from time to time, we have these mottled effects that bother our sense of intellectual esthetics. But if we know that the structure is sound and that we are protecting it against erosion, maybe we can afford to be less concerned about the frustrations that are bothering our sense of beauty. Neatness is not the order of the pharmaceutical day, but it never is in times of stress and change.

With respect to the course syllabi covered, I believe the majority of teachers agree that the bulk of the items listed should be brought into the curriculum at some point. Possibly an exception is the more controversial fourth course, which is admitted to be and intended to be provocative. The unsettled points rest upon sequence, prerequisites (to a limited degree), depth, and many other factors in the various schools.

With respect to the first course, my own comment is a reminder that it still is necessary to walk before you run, and it would seem to be necessary to lay same less esoteric background before moving too deeply into the more quantitative aspects of "physical pharmacy". I would not like to plead for too much simplicity, however, for I am mindful of several important things to be taken into consideration such as (1) the relative maturity of the student who may be a "screened in" college junior when he takes his first pharmacy course, (2) the breadth of basic science background of the student at that time, and (3) the personal belief that students can be challenged with more difficult material than we often believe if the instructor is careful in his plans and skillful in his presentation. It would seem to be possible to lay the basis for greater sophistication here, perhaps, in the same sense that modern general chemistry lays the basis for physical chemistry.

The second course, ostensibly physical pharmacy, will have to be left to the judgment, background and interests of each individual teacher. To those of you who have not yet prepared your syllabi for such a course and who feel a bit at sea, let me remind you that the numbers of such separate and distinct courses now actually being taught to undergraduates probably can be counted on the fingers of one hand, and many of the strongest advocates of the course are not now teaching it. This being the case, you need have no concern that your proposals will be badly out of line for the line is short and ill-defined.

It is evident that both breadth and depth in this course are a matter of concern, and part of that concern seems to be tied up with the question of how the practicing pharmacist can use this material and if there is a danger in overtraining the undergraduate.

As far as community and general practice is concerned, it seems clear that the professionalization of pharmaceutical service is absolutely essential if pharmacy is to survive in anything like its present form. As has been pointed out by Dr. Autian, part of that service is advisement relative to the pharmaceutical properties of drugs. To everyone here, it surely must be clear that today no one can talk discriminatingly about the pharmacy of today's medicaments without some knowledge of the intricacies of such factors as tonicity, biological half-life, equilibria, and the like. If not the more sophisticated quantitative aspects, surely a qualitative and descriptive understanding and quasi-quantitative approach should be inculcated in the minds of our students. Again the matter of depth must be left to individual teachers.

While the third course, as described by Dr. Parrott, introduces, at least, the question of the desirability of integration vs. separation of the applied phases from the more basic phases of physical pharmacy, it would seem clear enough that without application one way or the other, the purpose of the whole thing would really break down. Again the organization, depth, and breadth of the course would have to be determined by the individual instructor, and many circumstances, largely geographic, will determine its integrative nature.

The fourth course, as presented, is the most controversial and purposely so. I hope the fact that relatively less discussion has taken place around it during the seminar is not an indication of lack of interest or failure to appreciate its importance. I do not interpret it this way, but rather I assume that since much of the proposed outline revolves around integration of nearly all of the curriculum directed away from the sharply technical toward the professional, there is a natural inclination to shy away from the topic in a seminar on the "technical pharmacy courses." Nevertheless, it is the speaker's personal opinion that many of the explicit and implicit points brought out by the speaker and the discussants need the treatment of nearly an entire general seminar.

At the very time when the pharmacist has been hit hardest by the industrial revolution, we find social and economic forces of great magnitude squeezing in on him, too. In this crucial period, all too few are the serious attempts to study this situation free from emotion and with the tools of others than the biological and physical scientists.

The new role of the pharmacist, in part, is an advisory and consultative one as projected by many. To a certain degree, I would say a major degree, the pharmacy student now and certainly in the extended program, has the major elements of background for this, but in my own mind he is not too well prepared to transfer this knowledge to the task. So many psychological studies have been made showing the difficulty in applying knowledge not already brought to bear on specific type problems for the student that when one remembers we are dealing with average students, I doubt if we can expect the student to be prepared for this role without the development of techniques for this purpose. My general observation about the validity of the assumption, by one specialist, that certain information is definitely taught, and in a useful manner, by another specialist, leads me to question whether many of the items suggested by Dr. Autian are really available now to the student in a form very useful for this consultative purpose. In a sense, we are asking the student pharmacist to function differently or at least to be more conscious of the newer roles in an atmosphere in which he sees little of a model in the present practitioner and so needs expert guidance, particularly now. It must be made clearer, both to the practitioner and the public, precisely what the professional role above and beyond the "count out—pour out" stage really is.

Possibly one reason that so little attention has been given to this matter is that "what is everybody's business is nobody's business." This matter needs the conscious effort of every one of the pharmaceutical areas and someone must take the leadership or it is apt not to be done.

To recapitulate this portion of the summary, the following might be said:

(1) It appears to be an unquestioned fact that the physical, less descriptive aspects of pharmaceutical technology are becoming rapidly the center of scientific pharmacy.

(2) Certain simpler, more descriptive aspects need to be touched upon at least in the earlier levels of professional instruction.
(3) At the undergraduate level, the breadth and depth of these approaches must be determined by the individual instructor in light of such factors as the character of basic science backgrounds and professional science offerings to which the student has been subjected as well as the instructor's own background.
(4) There needs to be conscious effort to participate more actively in redefinition of the professional pharmaceutical function to the student.

Since others are evaluating the four courses, in reality the workshop sessions, I will not say anything about them other than that the plan has been good and the discussions often spirited and useful. If there is a fault, it is perhaps that there should have been more workshop sessions to allow for further discussion.

In closing, it has been fun, it has been profitable and, we hope, productive. It might be well to remind ourselves of Dr. Briggs' quotation from Robert Hutchins. "There is a steady slide toward intellectual inertia. We must commit ourselves to the idea of continuing education throughout our lives. Education is not a misfortune endured in childhood, which you need not, indeed cannot, have again. Education is the continuous development of our highest powers. It is too good a thing to be left to children."

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